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(54) Title: UTILIZATION OF FPRL1 AS A FUNCTIONAL RECEPTOR BY SERUM AMYLOID A (SAA)

(57) Abstract: The present invention relates to the discovery that serum amyloid A (SAA) is a ligand for the FPRL 1 receptor. Disclosed herein, are novel biological tools for the study of SAA/FPRL1 complex assembly and prophylactics, therapeutics, and methods of use of the foregoing, which modulate the association of SAA with FPRL1 and thereby effect responses including, but not limited to, signal transduction, chemotaxis, leukocyte migration, immune system response, amyloidosis, inflammatory response, infection, organ rejection, arthritis, atherosclerosis, and neoplasia.



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UTILIZATION OF FPRL1 AS A FUNCTIONAL RECEPTOR BY SERUM AMYLOID A (SAA)

FIELD OF THE INVENTION

The present invention relates to the discovery that serum amyloid A (SAA) is a ligand for the FPRL1 receptor. Disclosed herein are novel biological tools for the study of SAA/FPRL1 complex assembly and prophylactics, therapeutics, and methods of use of the foregoing, which modulate the association of SAA with FPRL1 and thereby effect cellular responses.

BACKGROUND OF THE INVENTION

Serum amyloid A (SAA), an acute phase protein, is normally present in serum at 0.1 μ M levels, but increases by 1000 fold in systemic inflammatory conditions. (Sipe, J.D., Immunophysiology: The role of cells and cytokines in immunity and inflammation, 259-273 (1990); Kisilevsky, R., *Medical Hypotheses*, 35:337-341 (1991); Skinner, M., *J. Intern. Med.*, 232:513-514 (1992); and Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)). It has been proposed that SAA is involved in lipid transportation and metabolism. (Sipe, J.D., Immunophysiology: The role of cells and cytokines in immunity and inflammation, 259-273 (1990); Kisilevsky, R., *Medical Hypotheses*, 35:337-341 (1991); and Skinner, M., *J. Intern. Med.*, 232:513-514 (1992)). Chronic inflammatory conditions with elevated serum SAA can culminate in amyloidosis, characterized by deposition of "amyloid" fibrils in tissues and associated with progressive destruction of organ function. (Kisilevsky, R., *Medical Hypotheses*, 35:337-341 (1991); Skinner, M., *J. Intern. Med.*, 232:513-514 (1992); and Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)). Although a number of acute phase proteins are known to modulate host immune responses, recombinant human (rh) SAA has exhibited chemoattractant activity for human monocytes, neutrophils and T lymphocytes *in vitro*. (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); and Xu et al., *J. Immunol.*, 155:1184-1190 (1995)). Further, rhSAA induces infiltration of phagocytic cells and T lymphocytes into injection sites in mice. (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); and Xu et al., *J. Immunol.*, 155:1184-1190 (1995)). Thus, many in the art recognize that SAA plays a role in cellular responses including, but not limited to, leukocyte migration, immune system response, amyloidosis, inflammatory response, infection, organ rejection, arthritis, atherosclerosis, and neoplasia.

Since SAA induces significant Ca^{2+} mobilization in phagocytes (Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)) and both its chemotactic and Ca^{2+} mobilizing effects are inhibited by pretreatment with pertussis toxin, SAA is thought to mediate cellular responses through G-protein-coupled receptors. (Xu et al., *J. Immunol.*, 155:1184-1190 (1995); and Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)). Despite considerable effort, however, investigators have failed to identify the SAA receptor on human phagocytic cells that mediate the aforementioned cellular responses.

BRIEF SUMMARY OF THE INVENTION

The acute phase protein serum amyloid A (SAA) is a potent chemoattractant for human leukocytes *in vitro* and mouse phagocytes *in vivo*. To identify the signaling mechanisms, we have evaluated patterns of cross-desensitization between SAA and other leukocyte chemoattractants. During these studies, we discovered that high concentrations of the chemotactic bacterial peptide, N-formyl-methionyl-leucyl-phenylalanine (fMLP), was able to specifically attenuate SAA induced Ca^{2+} mobilization in human phagocytes. With this data in hand, we realized that SAA uses a low affinity fMLP receptor.

Further investigation revealed that SAA selectively induces Ca^{2+} mobilization and migration of cells that were transfected to express a seven-transmembrane G protein coupled receptor, FPRL1. FPRL1 is a human phagocyte receptor with low affinity for fMLP and a high affinity for lipoxin A4, a lipid mediator. More evidence that FPRL1 was the SAA receptor on human phagocytes was obtained from experiments that characterized the ability of radiolabeled SAA to bind to human phagocytes and 293 cells transfected to express FPRL1. In these studies, we found that SAA exhibits a high affinity for the FPRL1 receptor but is not a ligand or agonist for the high affinity fMLP receptor, FPR. Significantly, over the course of several experiments, we have discovered that a SAA/FPRL1 complex can mediate signal transduction, leukocyte migration and activation, which account for the many activities of SAA in immune system response, amyloidosis, inflammatory response, infection, organ rejection, arthritis, atherosclerosis, and neoplasia.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 Cross-desensitization of Ca^{2+} mobilization in human monocytes between SAA and fMLP. Fura-2 loaded monocytes were sequentially stimulated with SAA and fMLP (panel A) or vice versa (panel B and C), and the ratio of fluorescence at 340 and 380 nm wavelength was recorded and calculated with the FLWinLab program.

FIGURES 2A-2E Calcium mobilization in FPRL1 transfected HEK 293 cells. FPRL1/293 cells were loaded with Fura-2 and were stimulated with various concentrations of fMLP (FIGURE 2A) or SAA (FIGURE 2B). SAA does not induce Ca^{2+} mobilization in FPR expressing 293 cells or mock transfected 293 cells (FIGURES 2C-2D). FIGURE 2E shows the sequential stimulation of FPRL1/293 cells with SAA and fMLP or vice versa.

FIGURES 3A-3C Chemotactic activity of SAA for human monocytes and cells transfected to express chemoattractant receptors. Different concentrations of SAA were placed in the lower wells of the chemotaxis chamber. Monocytes, FPRL1/293 cells or FPR expressing ETFR cells were placed in the upper wells. After incubation, the cells migrated across the polycarbonate filter were counted and photographed; SAA 0.8 μM , fMLP 100 nM. The cell migration was expressed as chemotaxis index representing the fold increase of the cells migrating in response to stimulants over control medium. FIGURE 3A: migration of FPRL1/293 cells in response

to SAA and fMLP. FIGURE 3B: migration of FPR expressing ETFR cells in response to SAA and fMLP. FIGURE 3C: effect of HDL on SAA induced FPRL1/293 cell migration. HDL at 1000 µg/ml mixed with 0.8 µM SAA was preincubated at 37°C for 4 h. The mixture was then tested for chemotactic activity on FPRL1/293 cells. The HDL/SAA mixture without preincubation was also tested for chemotactic activity and yielded similar results.

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FIGURE 4 Binding of ¹²⁵I-SAA to human monocytes and FPRL1/293 cells. rhSAA was radio-iodinated by the chloramine T method and the binding of ¹²⁵I-SAA to FPRL1/293 cells (panel A) or monocytes (panel B) was measured by adding a constant concentration of ¹²⁵I-SAA to the cells in the presence of increasing concentrations of unlabeled SAA. The data was analyzed and plotted using LIGAND software on a Macintosh computer. Panel C shows the displacement of ¹²⁵I-SAA binding on monocytes by unlabeled SAA and fMLP. Same results were obtained with FPLR1/293 cells (panel D).

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DETAILED DESCRIPTION OF THE INVENTION

In the disclosure herein, we describe the discovery of the SAA receptor on human phagocytes (FPRL1) and teach that modulation of the SAA/FPRL1 complex can influence cellular responses including, but not limited to, signal transduction, leukocyte migration, immune system response, amyloidosis, inflammatory response, infection, organ rejection, arthritis, atherosclerosis, and neoplasia. Novel biological tools for the study of the interaction of SAA, fragments of SAA, or homologs or derivatives thereof with FPRL1 are provided. Further, prophylactics, therapeutics, and methods of use of the foregoing, which modulate the association of SAA with FPRL1 and thereby effect the cellular responses described above, are taught.

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We began the search that led to the discovery of the SAA/FPRL1 complex by investigating the effects of SAA and other chemoattractants on Ca²⁺ mobilization in monocytes and neutrophils. In primary cells, cross-desensitization of Ca²⁺ transients is often due to two agonists acting at the same receptor. (Wang et al., *J. Exp. Med.*, 177:699-705 (1993)). During cross-desensitization experiments using SAA and other chemoattractants, we found that the bacterial chemotactic peptide N-formyl-methionyl-leucyl-phenylalanine (fMLP), when used at relatively high concentrations (10 µM and more), was able to attenuate a subsequent cell response to SAA. These results led us to believe that SAA interacts with a low affinity fMLP receptor on leukocytes.

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To date, two receptors that bind fMLP have been identified and cloned. (*Reviewed in* Prossnitz, E.R. and R.D. Ye, *Pharmacol. Ther.*, 74:73-102 (1997); and Murphy, P.M., Chemoattractant ligands and their receptors, pp. 269 (1996)). The prototype receptor, FPR, binds fMLP with high affinity and is activated by low concentrations of fMLP. Another highly homologous variant of FPR, named FPRL1 (also referred to as FPRH2 and LXA4R), was originally cloned as an orphan receptor (Murphy et al., *J. Biol. Chem.*, 267:7637-7643 (1992); Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); Bao et al., *Genomics*, 13:437-440 (1992); Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993); and Nomura et al., *Int.*

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Immunol., 5:1239-1249 (1993)) but was subsequently found to mediate Ca^{2+} mobilization in response to high concentrations of fMLP. (Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); and Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993)). Furthermore, a lipid metabolite, lipoxin A4 and its analogues, were found to bind FPRL1 with high affinity and increase arachidonic acid production and G-protein activation in FPRL1 transfected cells. (Fiore et al, *J. Exp. Med.*, 180:253-260 (1994)).

LXA4 inhibits pro-inflammatory neutrophil responses (Fiore et al, *J. Exp. Med.*, 180:253-260 (1994); Takano et al., *J. Exp. Med.*, 185:1693-1704 (1997); Maddox et al., *J. Biol. Chem.*, 272:6972-6978 (1997); Fiore et al., *Blood*, 81:3395-3403 (1993); Fiore, S. and C.N. Serhan, *Biochemistry*, 34:16678-16686 (1995); Gronert et al., *J. Exp. Med.*, 187:1285-1294 (1998); Gewirtz et al., *J. Clin. Invest.*, 101:1860-1869 (1998); Romano et al., *J. Immunol.*, 157:2149-2154 (1994); and Colgan et al., *J. Clin. Invest.*, 92:75-82 (1993)) as well as the release of the proinflammatory cytokine, IL-8 by epithelial cells. (Gronert et al., *J. Exp. Med.*, 187:1285-1294 (1998); and Takano et al., *J. Clin. Invest.*, 101:819-826 (1998)). These cellular responses have been attributed to activation of FPRL1 (or LXA4R) in neutrophils and epithelial cells.

Another lipid mediator receptor, the leukotriene B4 (LTB4) receptor, is structurally related to FPRL1 (30.7% amino acid sequence identity) (Yokomizo et al., *Nature*, 387:620-624 (1997)), and has also been reported to be a fusion co-factor for human immunodeficiency virus type I (HIV-1) (Owman et al., *Proc. Natl. Acad. Sci. U S A.*, 95:9530-9534 (1998)), similar to various chemokine receptors (reviewed in ref. Berger, E.A., *AIDS*, 11:S3-16 (1997)). This activity has not been reported for FPRL1, however. (Murphy, P.M., *Chemoattractant ligands and their receptors*, pp. 269 (1996); and Berger, E.A., *AIDS*, 11:S3-16 (1997)).

Because our cross de-sensitization experiments provided evidence that a low affinity fMLP receptor interacted with SAA, we performed chemotactic assays and radioactive SAA binding studies on cells that were transfected to express different receptors. In one experiment, for example, we selectively induced Ca^{2+} mobilization by administering SAA and observed the migration of cells that were transfected to express FPRL1 receptors, which were not endogenous to these cell types. In another experiment, we found that radiolabeled SAA bound to FPRL1 but not the FPR receptor. Through these investigations, we have discovered a novel interaction between FPRL1 and SAA.

By enhancing or inhibiting ("modulating") assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction, cellular responses such as signal transduction, leukocyte migration, immune system response, amyloidosis, inflammatory response, infection, organ rejection, arthritis, atherosclerosis, and neoplasia can be selectively altered. In some aspects of the invention, the modulation of the assembly of the SAA/FPRL1 complex is accomplished by using a modulator that is a nucleic acid embodiment. For example, a construct encoding FPRL1 is transfected into cells so as to raise the concentration of FPRL1 and thereby promote SAA/FPRL1 complex assembly or, alternatively, a construct encoding a nucleic acid that is complementary to a nucleic acid encoding FPRL1 (e.g., an antisense inhibitor or a ribozyme) is used to reduce the concentration of FPRL1 and thereby inhibit SAA/FPRL1 assembly. Further, in some embodiments, nucleic acids encoding wild-type or mutant SAA or fragments of SAA or complements of these nucleic acid molecules

are transfected into cells so as to modulate SAA/FPRL1 complex assembly and/or SAA/FPRL1-mediated signal transduction.

According to other aspects, the modulation of the assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction is achieved by using a modulator that is a protein-based embodiment. For example, FPRL1 or fragments thereof can be delivered to cells by liposome-mediated transfer or administered to cells exogenously so as to modulate assembly of the SAA/FPRL1 complex or, alternatively, wild-type or mutant SAA, or fragments thereof can be administered to cells so as to modulate assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. Peptidomimetics that resemble SAA or FPRL1 or fragments thereof are also modulators of the invention and can be used to effect assembly of the SAA/FPRL1 complex. Many chemicals can also be modulators and can be identified by their ability to effect assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction using the SAA/FPRL1 characterization assays described below. These embodiments can be manufactured as monomeric, multimeric, and multimerized agents.

Several types of assays that provide information about SAA or FPRL1 or the formation of the SAA/FPRL1 complex are embodiments of the invention. These assays are collectively referred to as "SAA/FPRL1 characterization assays". One type of SAA/FPRL1 characterization assay concerns measuring the ability of SAA or fragments thereof to bind to FPRL1 or vice versa. For example, methods of performing SAA/FPRL1 characterization assays are provided, in which FPRL1 or SAA are disposed on a support and are subsequently contacted with a ligand (e.g., SAA or FPRL1 or a fragment thereof, depending on the support-bound molecule) and assembly of the SAA/FPRL1 complex is determined. A similar binding assay can be employed in the presence of an inhibiting or enhancing molecule (a "modulator") such as a peptide or peptidomimetic (collectively referred to as a "peptide agent") or a chemical. The supports in these assays can be conventional resins, plastics, lipids, membranes, and cells.

Other aspects of the invention utilize software and hardware comprising nucleic acid sequences encoding SAA or FPRL1 or fragments thereof or complements of these sequences and protein sequences corresponding to SAA or FPRL1 or fragments thereof. Aspects of the invention also utilize software and hardware having the aforementioned sequences to characterize two dimensional and three dimensional aspects of SAA and FPRL1, which allows one to develop protein models of SAA and FPRL1, identify homologous proteins, and conduct rational drug design. Methods of identification of agents that modulate assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction, for example, use software and hardware that have the aforementioned sequence information.

The embodied approaches to rational drug design seek to identify novel agents that interact with SAA or FPRL1 and modulate assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. Accordingly, protein models of SAA or FPRL1 or fragments of these molecules, and models of candidate modulating agents are constructed and combinatorial chemistry is employed to develop and identify agents that modulate assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. Once

candidate agents are developed and identified, they are screened in a SAA/FPRL1 characterization assay (e.g., a SAA adhesion assay). The identity of each agent and its performance in a SAA/FPRL1 characterization assay, e.g., its effect on the modulation assembly of the SAA/FPRL1 complex, can be recorded on software or hardware and the recorded data can be used to create a library of SAA/FPRL1 modulating agents. These libraries can be employed to identify more agents that modulate assembly of the SAA/FPRL1 complex and are valuable clinical tools for manufacturing and selecting an appropriate pharmaceutical to treat a particular type of malady.

In the therapeutic and prophylactic embodiments of the invention, SAA or FPRL1, polypeptide fragments of SAA or FPRL1, and nucleic acids encoding these molecules, and agents that interact with a SAA/FPRL1 complex are incorporated into pharmaceuticals. These pharmaceuticals can be delivered by any conventional route including, but not limited to, transdermal, parenteral, gastrointestinal, transbronchial, and transalveolar. In addition to the active ingredients mentioned above, the pharmaceutical embodiments can comprise carriers, proteins, supports, adjuvants, or components that facilitate or enhance drug delivery. These pharmaceuticals can be employed in therapeutic protocols for the treatment and prevention of a SAA-related malady (e.g., an abnormal immune system response, amyloidosis, inflammation, infection, organ rejection, arthritis, atherosclerosis, and neoplasia). By one approach, a subject at risk for contracting a SAA-related malady or a subject already afflicted with a SAA-related malady is identified by conventional techniques and then is administered an effective amount of an agent that inhibits or promotes assembly of the SAA/FPRL1 complex. The discovery of the SAA/FPRL1 complex is disclosed in the following section.

Discovery of the SAA receptor on human leukocytes

In a series of cross-desensitization experiments, we observed that SAA at 1 μ M failed to desensitize the Ca^{2+} flux in monocytes or neutrophils induced by chemokines such as MCP-1, RANTES, MCP-3, MIP-1 α , IL-8 and SDF-1 α . We concluded from these findings that SAA was unlikely to share a receptor with any of the chemokines tested. Additionally, we observed that SAA did not attenuate the cell response to the bacterial chemotactic N-formylated peptide fMLP, when fMLP was used at 100 nM (10^{-7} M) (FIGURE 1A). In reciprocal tests, however, fMLP at 100 nM showed a partial desensitizing effect on SAA-induced Ca^{2+} mobilization in monocytes (FIGURE 1B). The cellular response to SAA was completely desensitized by higher concentrations of fMLP (10^{-3} M = 1 mM, FIGURE 1C), providing evidence that SAA uses a low affinity fMLP receptor(s).

Since fMLP was known to induce Ca^{2+} mobilization in phagocytes through at least two seven transmembrane, G-protein-coupled receptors, FPR and FPRL1 (Murphy et al., *J. Biol. Chem.*, 267:7637-7643 (1992); Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993); and Murphy, P.M. and D. McDermott, *J. Biol. Chem.*, 266:12560-12567 (1991)), we tested the effect of SAA using cells transfected to express these receptors. Prior to transfection, these cells were not responsive to fMLP stimulation. In the FPR-transfected rat basophil leukemia cell line

(ETFR cells), we observed Ca^{2+} mobilization over a wide range of fMLP concentrations, with an EC₅₀ of 10 pM. In contrast, the EC₅₀ for fMLP to induce Ca^{2+} mobilization in FPRL1 transfected cells (FPRL1/293 cells) was much higher at 10 μM (FIGURE 2A). These results confirmed earlier observations that FPR is a high affinity receptor for fMLP, whereas FPRL1 has a much lower affinity. (Murphy et al., *J. Biol. Chem.*, 267:7637-7643 (1992); Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993); and Murphy, P.M. and D. McDermott, *J. Biol. Chem.*, 266:12560-12567 (1991)).

Further, rhSAA induced Ca^{2+} mobilization in cells transfected with FPRL1 (FPRL1/293 cells) (FIGURE 2B), but not in FPR expressing cells or mock transfected 293 cells (FIGURE 2C, D). The EC₅₀ of rhSAA on FPRL1 transfected cells was 250 nM, suggesting that SAA activates FPRL1 with higher efficacy than fMLP. This was supported by studies of cross-desensitization of Ca^{2+} flux between SAA and fMLP in FPRL1/293 cells. As shown in FIGURE 2E, although sequential stimulation of FPRL1/293 cells with SAA and fMLP resulted in bidirectional desensitization, SAA was able to desensitize the cell response to a 100 fold excess of fMLP. In contrast, fMLP at 100 fold excess of SAA, only partially desensitized the effect of SAA (FIGURE 2E).

Leukocyte infiltration *in vivo* is believed to result from the migration of cells toward a gradient of locally produced chemoattractant(s). This process can be emulated by *in vitro* assays of chemotaxis, which provide a very sensitive and biologically relevant means of evaluating the function of cloned chemoattractant receptors. (Gong et al., *J. Biol. Chem.* 272:11682-11685 (1997); Wang et al., *J. Exp. Med.*, 177:699-705 (1993); Gong et al., *J. Biol. Chem.*, 272:11682-11685 (1997); and Ben-Baruch et al., *J. Biol. Chem.* 270:22123-22128 (1995)). Since SAA was known to induce leukocyte infiltration *in vivo* (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); and Xu et al., *J. Immunol.*, 155:1184-1190 (1995)) and chemotaxis *in vitro* (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); and Xu et al., *J. Immunol.*, 155:1184-1190 (1995)), we sought to determine whether SAA could induce cell migration via FPRL1.

In our experiments on SAA induced chemotaxis in FPRL1/293 cells, we discovered that FPRL1/293 cells exhibit a potent migratory response to SAA, having an EC₅₀ of 200 nM. Remarkably, these cells failed to migrate in response to a wide range of concentrations of fMLP (FIGURE 3A). The fMLP induced migration of FPR expressing ETFR cells occurred at nM range concentrations, whereas the same cells did not migrate in response to SAA (FIGURE 3B). These chemotaxis experiments established that fMLP is only a partial agonist for FPRL1 since the ligand failed to induce cell migration through FPRL1. On the other hand, SAA demonstrated full agonist activity on FPRL1. Further, both SAA induced Ca^{2+} mobilization and chemotaxis in FPRL1/293 cells were inhibited by pretreatment of the cells with pertussis toxin but not cholera toxin, which correlates with observations in native cells (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); Xu et al., *J. Immunol.*, 155:1184-1190 (1995); and Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)).

Additionally, we examined the effect of HDL on the chemotactic activity of SAA for FPRL1/293 cells. SAA can form complexes with HDL and HDL is a natural inhibitor of SAA. (Badolato et al., *J. Exp. Med.*,

180:203-209 (1994); and Xu et al., *J. Immunol.*, 155:1184-1190 (1995)). FIGURE 3C shows that HDL, whether preincubated with SAA or simultaneously added to SAA, completely abolished SAA-induced FPRL1/293 cell migration. In contrast, the same concentration of HDL did not affect migration of FPR expressing ETFR cells induced by fMLP. These results confirmed that HDL specifically inhibited the agonist activity of SAA on FPRL1.

To further verify that FPRL1 is the SAA receptor, we performed ligand binding experiments. FIGURE 4 shows that radioiodinated SAA specifically bound to FPRL1/293 cells with an estimated k_d at 64 nM and 42000 binding sites/cell (FIGURE 4A). ^{125}I -SAA also specifically bound to monocytes (FIGURE 4B) and neutrophils (K_d = 45 nM, R = 6700/cell) with K_d values comparable to those achieved with FPRL1/293 cells. In the displacement assay, unlabeled SAA inhibited its own binding to monocytes (FIGURE 4C), neutrophils and FPRL1/293 (FIGURE 4D) in a dose-dependent manner, having an IC_{50} at about 50 nM. In contrast, unlabeled fMLP at high concentrations (10 μM) only partially competed with ^{125}I -SAA for binding. These results demonstrated that SAA is a far more efficient agonist for FPRL1 than fMLP.

In the experiments presented above, we have established that SAA associates with FPRL1, a seven-transmembrane, G-protein coupled receptor that is expressed on phagocytes and promotes chemotaxis. (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); Xu et al., *J. Immunol.*, 155:1184-1190 (1995); and Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)). We have discovered that SAA mediates cellular responses by forming a complex with FPRL1. Although FPRL1 had previously been shown to be a low affinity receptor for fMLP (Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); and Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993)) and a high affinity receptor for lipid metabolite LXA4 and its analogues (Fiore et al., *J. Exp. Med.*, 180:253-260 (1994); Takano et al., *J. Exp. Med.*, 185:1693-1704 (1997); Maddox et al., *J. Biol. Chem.*, 272:6972-6978 (1997); Fiore et al., *Blood*, 81:3395-3403 (1993); Fiore, S. and C.N. Serhan, *Biochemistry*, 34:16678-16686 (1995); Gronert et al., *J. Exp. Med.*, 187:1285-1294 (1998); Gewirtz et al., *J. Clin. Invest.*, 101:1860-1869 (1998); Romano et al., *J. Immunol.*, 157:2149-2154 (1994); Colgan et al., *J. Clin. Invest.*, 92:75-82 (1993); and Takano et al., *J. Clin. Invest.*, 101:819-826 (1998)), until the present disclosure, it was not known that SAA interacts with FPRL1. Unlike fMLP, which is a partial agonist incapable of inducing chemotaxis via FPRL1, SAA is the first chemotactic agonist produced in humans identified for FPRL1.

FPRL1 was identified and molecularly cloned from human phagocytic cells by low stringency hybridization of the cDNA library with the FPR sequence and was initially defined as an orphan receptor. (Murphy et al., *J. Biol. Chem.*, 267:7637-7643 (1992); Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993); and Nomura et al., *Int. Immunol.*, 5:1239-1249 (1993)). The cloning of the same receptor termed FPRH2 from a genomic library was described by Bao et al. (Bao et al., *Genomics*, 13:437-440 (1992)). FPRL1 possesses 69% identity at the amino acid level to FPR, the prototype receptor for synthetic and bacterium-derived formylated peptides (Prossnitz,

E.R. and R.D. Ye, *Pharmacol. Ther.*, 74:73-102 (1997); and Murphy, P.M., Chemoattractant ligands and their receptors, pp. 269 (1996)). Both FPR and FPRL1 are expressed by monocytes and neutrophils and are clustered on human chromosome 19q13. (Bao et al., *Genomics*, 13:437-440 (1992); and Durstin et al., *Biochem. Biophys. Res. Commun.*, 201:174-179 (1994)). While fMLP is a high affinity agonist for FPR, it interacts with
5 FPRL1 and transduces signals in response to fMLP only at high concentrations. (FIGURE 2 and ref: Ye et al., *Biochem. Biophys. Res. Commun.*, 184:582-589 (1992); Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401 (1993); and Durstin et al., *Biochem. Biophys. Res. Commun.*, 201:174-179 (1994)). SAA, on the other hand, selectively binds and activates FPRL1 at physiologically relevant concentrations, which under inflammatory stimulation could reach 80 μ M in the serum. (Sipe, J.D., Immunophysiology: The role of
10 cells and cytokines in immunity and inflammation, 259-273 (1990); Kisilevsky, R., *Medical Hypotheses*, 35:337-341 (1991); Skinner, M., *J. Intern. Med.*, 232:513-514 (1992); and Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)).

FPRL1 is predominantly expressed in monocytes and neutrophils. However, cells other than phagocytes such as hepatocytes have also been shown to express FPRL1. (Prossnitz, E.R. and R.D. Ye, *Pharmacol. Ther.*, 74:73-102 (1997)). Recently, the expression of this receptor (also termed LXA4R) has been
15 reported to be highly inducible in epithelial cells by specific cytokines. (Gronert et al., *J. Exp. Med.*, 187:1285-1294 (1998)). Our previous study demonstrated that CD3⁺ human peripheral blood T lymphocytes were induced by SAA to migrate and adhere to endothelial cell monolayers. (Xu et al., *J. Immunol.*, 155:1184-1190 (1995)). In fact, we detected specific binding sites for ¹²⁵I-SAA on human peripheral blood CD3⁺ T lymphocytes (K_d=300 nM, R=2200 sites/cell). Whether these binding sites on T lymphocytes represent
20 FPRL1 or additional receptor(s) for SAA was not known until the present disclosure.

While the chemotactic formyl peptide fMLP has been shown to be a low efficiency agonist for FPRL1, a lipid metabolite lipoxin A4 (LXA4) has been reported to be a high affinity ligand and potent agonist for this receptor. (Fiore et al, *J. Exp. Med.*, 180:253-260 (1994)). LXA4 is an eicosanoid generated during a number of
25 host reactions such as inflammation, thrombosis and atherosclerosis (Romano et al., *J. Immunol.*, 157:2149-2154 (1994)), and was initially discovered as an inhibitor of immune response. (*Reviewed in* Samuelsson et al., *Science*, 237:1171-1176 (1987)). LXA4 was subsequently reported to inhibit neutrophil chemotaxis (Lee et al., *Biochem. Biophys. Res. Commun.*, 180:1416-1421 (1991)) and transepithelial migration induced by chemotactic agents. (Colgan et al., *J. Clin. Invest.*, 92:75-82 (1993)). A seven transmembrane G-protein
30 coupled receptor identical to FPRL1 was recently identified for LXA4. (Fiore et al, *J. Exp. Med.*, 180:253-260 (1994); Takano et al., *J. Exp. Med.*, 185:1693-1704 (1997); and Romano et al., *J. Immunol.*, 157:2149-2154 (1994)). LXA4 bound with high affinity to CHO cells transfected with this receptor and increased GTPase activity and the release of esterified arachidonate. (Fiore et al, *J. Exp. Med.*, 180:253-260 (1994)).

LXA4 has been proposed to be an endogenously produced ligand for FPRL1. (Fiore et al, *J. Exp. Med.*,
35 180:253-260 (1994); and Takano et al., *J. Exp. Med.*, 185:1693-1704 (1997)). Although LXA4 has not been

reported to induce Ca^{2+} mobilization in neutrophils or FPRL1 transfected cells (Fiore et al., *J. Exp. Med.*, 180:253-260 (1994)), it was shown to induce Ca^{2+} flux and chemotaxis in monocytes. (Maddox et al., *J. Biol. Chem.*, 272:6972-6978 (1997); and Romano et al., *J. Immunol.*, 157:2149-2154 (1994)). In our present investigations, we did not detect a significant induction of Ca^{2+} flux or chemotaxis in FPRL1/293 cells using commercially available LXA4 (Biomol, Plymouth Meeting, PA), nor did we observe inhibition of SAA signaling or binding by this LXA4 in either phagocytes or FPRL1/293 cells.

Our previous studies also demonstrated that both SAA-induced leukocyte chemotaxis and activation were inhibited by pertussis toxin. (Xu et al., *J. Immunol.*, 155:1184-1190 (1995); and Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)). Furthermore, we have shown that signaling of SAA through FPRL1 was sensitive to pertussis toxin. Although the signal transduction pathways triggered by the interaction of SAA with FPRL1 are not yet fully understood, we believe that FPRL1 receptors share biochemical pathways with FPR. It is well known, for example, that binding of FPR by bacterium-derived or synthetic peptide agonists result in a G protein-mediated signaling cascade leading to phagocytic cell adhesion, chemotaxis, release of oxygen intermediates, enhanced phagocytosis and bacterial killing, as well as gene transcription. (Prossnitz, E.R. and R.D. Ye, *Pharmacol. Ther.*, 74:73-102 (1997); and Murphy, P.M., Chemoattractant ligands and their receptors, pp. 269 (1996)). Activation of FPR by its agonists can also result in heterologous desensitization of the subsequent cell response to other G-protein receptor ligands including chemokines. (Ali et al., *J. Biol. Chem.*, 268:24247-24254 (1993); and Ali et al., *J. Biol. Chem.*, 271:3200-3206 (1996)). We believe that a similar "desensitizing" effect of receptor activation can be present with FPRL1.

For instance, SAA was initially reported as an inhibitor of neutrophil response to fMLP. (Linke et al., *Biochem. Biophys. Res. Commun.*, 176:1100-1105 (1991)). In these experiments, neutrophils preincubated with SAA showed reduced superoxide release in response to fMLP. (Linke et al., *Biochem. Biophys. Res. Commun.*, 176:1100-1105 (1991)). Our previous study also demonstrated that preincubation of monocytes and neutrophils with SAA reduced cell response to a number of chemoattractants including fMLP and chemokines. (Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)). Accordingly, we believe that FPRL1 is capable of transducing intracellular biochemical responses leading to desensitization of other G-protein coupled receptors.

The optimal concentrations for SAA to induce leukocyte migration, adhesion and tissue infiltration range from 0.8 - 4 μM (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); Xu et al., *J. Immunol.*, 155:1184-1190 (1995); and Badolato et al., *J. Immunol.*, 155:4004-4010 (1995)), which are higher than the SAA levels present in normal serum but well below the concentration seen during a systemic acute phase response. (Sipe, J.D., Immunophysiology: The role of cells and cytokines in immunity and inflammation, 259-273 (1990); Kisilevsky, R., *Medical Hypotheses*, 35:337-341 (1991); Skinner, M., *J. Intern. Med.*, 232:513-514 (1992); and Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)). Increased serum levels of SAA have been observed in a number of inflammatory and infectious diseases as well as after organ transplantation. (Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)). The over-production of SAA by hepatocytes can

also be induced by inflammatory stimuli such as LPS, IL-1, IL-6 and TNF. (Sipe, J.D., Immunophysiology: The role of cells and cytokines in immunity and inflammation, 259-273 (1990); Kisilevsky, R., *Medical Hypotheses*, 35:337-341 (1991); Skinner, M., *J. Intern. Med.*, 232:513-514 (1992); and Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)). Additionally, macrophages have been reported to be an extra-hepatic source of SAA during inflammation (Steel et al., *Scand. J. Immunol.*, 44:493-500 (1996)) and can produce relatively high concentrations in microcompartments. The SAA concentrations required for activating FPRL1 are well within the range in which native cells are activated as shown by the results presented herein

The expression of SAA mRNA in human atherosclerotic lesions and the induction of SAA by oxidized low-density lipoproteins also support our belief that SAA plays an important role in vascular injury and atherosclerosis. (Malle, E. and F.C. De Beer, *Eur. J. Clin. Invest.*, 26:427-435 (1996)). Under normal conditions, most serum SAA will be associated with high density lipoprotein (HDL) which acts as a natural inhibitor of the chemotactic activity of SAA. (See Badolato et al., *J. Exp. Med.*, 180:203-209 (1994); and Xu et al., *J. Immunol.*, 155:1184-1190 (1995) and FIGURE 3D). However, since SAA binds to HDL at equimolar ratios (Liang, J. and J.D. Sipe, *J. Lipid Res.*, 36:37-46 (1995)), a rapid increase in concentration of locally produced SAA can establish a gradient of free active SAA with consequent recruitment of leukocytes into inflammatory sites. Desirably, an increase in concentration of SAA at local inflammatory sites can activate leukocytes to remove pathogenic agents. Furthermore, signals triggered by activated FPRL1 can result in unresponsiveness of leukocytes to additional stimulation, thus sequestering the cells, limiting the degree of inflammation, and providing therapeutic benefit. In the following section, several nucleic acid-based embodiments are provided.

Modulation of assembly of the SAA/FPRL1 complex using a nucleic acid agent

Full-length *SAA* and *FPRL1* (nucleic acids are represented in italics) and fragments of these molecules that encode polypeptides that are involved in the assembly of the SAA/FPRL1 complex are embodiments of the invention. Further embodiments include nucleic acids that complement full-length *SAA* and *FPRL1* and molecules that complement nucleic acids that encode polypeptides that are involved in the assembly of the SAA/FPRL1 complex. Desired embodiments include nucleic acids having at least 9 consecutive bases of *SAA* or *FPRL1* or a sequence complementary thereto, wherein the nucleic acid encodes a polypeptide that is involved in the assembly of the SAA/FPRL1 complex or wherein the nucleic acid complements a nucleic acid that encodes a polypeptide that is involved in the assembly of the SAA/FPRL1 complex. Preferably, the nucleic acid embodiments comprise at least 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides from *SAA* or *FPRL1* or a nucleic acid that complements *SAA* or *FPRL1*, as conditions dictate. More preferably, the nucleic acid embodiments comprise at least 20-30 consecutive nucleotides from *SAA* or *FPRL1* or a nucleic acid that complements *SAA* or *FPRL1*. In some cases, the nucleic acid embodiments comprise more than 30 nucleotides from the nucleic acids encoding *SAA* or *FPRL1* or a nucleic acid that complements these molecules and in other

cases, the nucleic acid embodiments comprise at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the nucleic acids encoding SAA or FPRL1 or a nucleic acid that complements these molecules.

The nucleic acid embodiments described above can be altered by mutation, such as substitutions, additions, or deletions, which provide for sequences encoding functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other DNA sequences that encode substantially the same SAA or FPRL1 amino acid sequence that is involved in the assembly of an SAA/FPRL1 complex can be used. These include, but are not limited to, nucleic acid sequences comprising all or portions of *SAA or FPRL1* or nucleic acids that complement all or part of *SAA or FPRL1* that have been altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Further, the nucleic acid embodiments of the invention can be used to modulate assembly of an SAA/FPRL1 complex and/or signal transduction (e.g., by upregulating or downregulating the expression of SAA or FPRL1) and, therefore, have several uses in biotechnological research and the treatment and prevention of disease. In the section below, several protein-based embodiments are provided.

Modulation of assembly of the SAA/FPRL1 complex using a peptide agent

In several embodiments of the present invention, SAA and FPRL1 and/or fragments thereof are incorporated into biotechnological tools and pharmaceuticals for therapeutic and prophylactic application. Preferably, the SAA and FPRL1 peptides and/or fragments thereof correspond to sequences involved in assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. Desirable peptides are between three amino acids and 100 amino acids in length and have at least some portion of the sequence of a peptide that is involved in assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. Additionally, peptidomimetics that resemble SAA and FPRL1 and fragments thereof or peptides of between three and 100 amino acids having sequence involved in assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction, are embodiments of the present invention. For example, an oligopeptide for use in aspects of the present invention can have three amino acids, four amino acids, five amino acids, six amino acids, seven amino acids, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty nine, or forty or fifty or sixty or seventy or eighty or ninety or one-hundred amino acids. Similarly, peptidomimetics of the present invention can have structures that resemble three amino acids, four amino acids, five amino acids, six amino acids, seven amino acids, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty nine, or forty or fifty or sixty or seventy or eighty or ninety or one-hundred amino acids.

Peptides for use in aspects of the present invention can also be modified, e.g., the peptides can have substituents not normally found on a peptide or the peptides can have substituents that are normally found on the peptide but are incorporated at regions of the peptide that are not normal. The peptides for use in aspects of the present invention can be acetylated, acylated, or aminated, for example. Substituents which can be included on the peptide so as to modify it include, but are not limited to, H, alkyl, aryl, alkenyl, alkynyl, aromatic, ether, ester, unsubstituted or substituted amine, amide, halogen or unsubstituted or substituted sulfonyl or a 5 or 6 member aliphatic or aromatic ring. As used throughout this disclosure, the term "peptide agent" refers to a modified or unmodified peptide and a chemical or a peptidomimetic that structurally (three-dimensionally or two-dimensionally) resembles a modified or unmodified SAA or FPRL1 or a fragment of these molecules. Peptide agents also include ligands identified by the methods of rational drug design detailed below.

The SAA and FPRL1 peptides and fragments or derivatives thereof, include but are not limited to, those containing as a primary amino acid sequence all or part of the amino acid sequence of SAA and FPRL1 found in nature. Additionally, altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change can also be present in the peptides of the invention. Accordingly, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity that acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence can be selected from other members of the class to which the amino acid belongs. For example, the non-polar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine. The uncharged polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine. The positively charged (basic) amino acids include arginine, lysine, and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. The aromatic amino acids include phenylalanine, tryptophan, and tyrosine. In other aspects of the invention, SAA and FPRL1 and fragments or derivatives thereof, which are differentially modified during or after translation, e.g., by phosphorylation, glycosylation, cross-linking, acylation, proteolytic cleavage, linkage to an antibody molecule, membrane molecule, or other ligand, are contemplated. (Ferguson et al., Ann. Rev. Biochem. 57:285-320 (1988)).

Many embodiments of the invention involve SAA or fragments of SAA or the use of these polypeptides or peptidomimetics that resemble the structures (collectively referred to as "peptide agents"). The polypeptide sequence of recombinant human SAA (rhSAA) is:

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRFFGRGAEDS
LADQAANEWGRSGKDPNHRPAGLPEKY (SEQ. ID. No. 1).

Carboxy truncations of SAA include:

- 5 MRS
- MRSF (SEQ. ID. NO. 2)
- MRSFF (SEQ. ID. NO. 3)
- 10 MRSFFS (SEQ. ID. NO. 4)
- MRSFFSF (SEQ. ID. NO. 5)
- 15 MRSFFSFL (SEQ. ID. NO. 6)
- MRSFFSFLG (SEQ. ID. NO. 7)
- MRSFFSFLGE (SEQ. ID. NO. 8)
- 20 MRSFFSFLGEA (SEQ. ID. NO. 9)
- MRSFFSFLGEAF (SEQ. ID. NO. 10)
- 25 MRSFFSFLGEAFD (SEQ. ID. NO. 11)
- MRSFFSFLGEAFDG (SEQ. ID. NO. 12)
- MRSFFSFLGEAFDGA (SEQ. ID. NO. 13)
- 30 MRSFFSFLGEAFDGAR (SEQ. ID. NO. 14)
- MRSFFSFLGEAFDGARD (SEQ. ID. NO. 15)
- 35 MRSFFSFLGEAFDGM (SEQ. ID. NO. 16)
- MRSFFSFLGEAFDGMW (SEQ. ID. NO. 17)
- MRSFFSFLGEAFDGMWR (SEQ. ID. NO. 18)
- 40 MRSFFSFLGEAFDGMWRA (SEQ. ID. NO. 19)
- MRSFFSFLGEAFDGMWRAY (SEQ. ID. NO. 20)
- 45 MRSFFSFLGEAFDGMWRAYS (SEQ. ID. NO. 21)
- MRSFFSFLGEAFDGMWRAYSD (SEQ. ID. NO. 22)
- MRSFFSFLGEAFDGMWRAYSDM (SEQ. ID. NO. 23)
- 50 MRSFFSFLGEAFDGMWRAYSDMR (SEQ. ID. NO. 24)

MRSFFSFLGEAFDGMWRAYSDMRE (SEQ. ID. NO. 25)

MRSFFSFLGEAFDGMWRAYSDMREA (SEQ. ID. NO. 26)

5 MRSFFSFLGEAFDGMWRAYSDMREAN (SEQ. ID. NO. 27)

MRSFFSFLGEAFDGMWRAYSDMREANY (SEQ. ID. NO. 28)

MRSFFSFLGEAFDGMWRAYSDMREANYI (SEQ. ID. NO. 29)

10 MRSFFSFLGEAFDGMWRAYSDMREANYIG (SEQ. ID. NO. 30)

MRSFFSFLGEAFDGMWRAYSDMREANYIGS (SEQ. ID. NO. 31)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSD (SEQ. ID. NO. 32)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDK (SEQ. ID. NO. 33)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKY (SEQ. ID. NO. 34)

20 MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYF (SEQ. ID. NO. 35)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFH (SEQ. ID. NO. 36)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHA (SEQ. ID. NO. 37)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHAR (SEQ. ID. NO. 38)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARG (SEQ. ID. NO. 39)

30 MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGN (SEQ. ID. NO. 40)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNY (SEQ. ID. NO. 41)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYD (SEQ. ID. NO. 42)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDA (SEQ. ID. NO. 43)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAA (SEQ. ID. NO. 44)

40 MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAK (SEQ. ID. NO. 45)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKR (SEQ. ID. NO. 46)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKRG (SEQ. ID. NO. 47)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKRGP (SEQ. ID. NO. 48)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKRPG (SEQ. ID. NO. 49)

50 MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKRPGG (SEQ. ID. NO. 50)

MRSFFSFLGEAFDGMWRAYSDMREANYIGSDKYFHARGNYDAAKRPGGV (SEQ. ID. NO. 51)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVW (SEQ. ID. NO. 52)

5 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWA (SEQ. ID. NO. 53)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAA (SEQ. ID. NO. 54)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAE (SEQ. ID. NO. 55)

10 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEA (SEQ. ID. NO. 56)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 57)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 58)

15 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 59)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 60)

20 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 61)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 62)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 63)

25 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 64)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 65)

30 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 66)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 67)

35 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 68)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 69)

40 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 70)

MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 71)

45 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 72)

50 MRSFFSFLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI (SEQ. ID. NO. 73)

- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAED
(SEQ. ID. NO. 73)
- 5 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
(SEQ. ID. NO. 74)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
L (SEQ. ID. NO. 75)
- 10 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LA (SEQ. ID. NO. 76)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LAD (SEQ. ID. NO. 77)
- 15 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQ (SEQ. ID. NO. 78)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQA (SEQ. ID. NO. 79)
- 20 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAA (SEQ. ID. NO. 80)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAAN (SEQ. ID. NO. 81)
- 25 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANE (SEQ. ID. NO. 82)
- 30 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEW (SEQ. ID. NO. 83)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWG (SEQ. ID. NO. 84)
- 35 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWGR (SEQ. ID. NO. 85)
- 40 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWGRS (SEQ. ID. NO. 86)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWGRSG (SEQ. ID. NO. 87)
- 45 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWGRSGK (SEQ. ID. NO. 88)
- MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKD (SEQ. ID. NO. 89)
- 50 MRSFFSFLGEAFDGARMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDP (SEQ. ID. NO. 90)

- MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPN (SEQ. ID. NO. 91)
- 5 MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNH (SEQ. ID. NO. 92)
- MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNH (SEQ. ID. NO. 93)
- 10 MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFR (SEQ. ID. NO. 94)
- MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRP (SEQ. ID. NO. 95)
- 15 MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPA (SEQ. ID. NO. 96)
- MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPAG (SEQ. ID. NO. 97)
- 20 MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPAGL (SEQ. ID. NO. 98)
- MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPAGLP (SEQ. ID. NO. 99)
- 25 MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPAGLPE (SEQ. ID. NO. 100)
- MRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPAGLPEK (SEQ. ID. NO. 101)
- 30
- 35 Amino truncations of SAA include:
- RSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSL
ADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 102)
- 40 SFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLA
DQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 103)
- FFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLAD
QAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 104)
- 45 FSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQ
AANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 105)
- SFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQA
ANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 106)
- 50 FLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 107)

- LGEAFDGMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 108)
- 5 GEAFDGMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
EWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 109)
- EAFDGMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 110)
- 10 AFDGMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 111)
- 15 FDGMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 112)
- DGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 113)
- 20 GARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 114)
- 25 ARDMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 115)
- RDMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 116)
- 30 DMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 117)
- MWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 118)
- 35 WRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 119)
- 40 RAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 120)
- YSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 121)
- 45 SDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 122)
- DMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 123)
- 50 MREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 124)

REANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLP
EKY (SEQ. ID. NO. 125)

5 EANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPE
KY (SEQ. ID. NO. 126)

ANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEK
Y (SEQ. ID. NO. 127)

10 NYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 128)

YIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 129)

15 IGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 130)

GSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 131)

20 SDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ.
ID. NO. 132)

25 DKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ.
ID. NO. 133)

KYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ.
ID. NO. 134)

30 YFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID.
NO. 135)

FHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID.
NO. 136)

35 HARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID.
NO. 137)

40 ARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO.
138)

RGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO.
139)

45 GNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO.
140)

NYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 141)

50 YDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 142)

DAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 143)

AAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 144)

AKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 145)

5 KRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 146)

RGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 147)

10 GPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 148)

PGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 149)

GGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 150)

15 GVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 151)

VWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 152)

20 WAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 153)

AAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 154)

AEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 155)

25 EAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 156)

AI SNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 157)

30 ISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 158)

SNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 159)

NARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 160)

35 ARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 161)

RENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 162)

40 ENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 163)

NIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 164)

IQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 165)

45 QRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 166)

RFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 167)

50 FFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 168)

GRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 169)

5 RGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 170)
GAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 171)
AEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 172)
EDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 173)
10 DSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 174)
SLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 175)
LADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 176)
15 ADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 177)
DQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 178)
QAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 179)
20 AANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 180)
ANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 181)
25 NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 182)
EWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 183)
WGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 184)
30 GRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 185)
RSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 186)
35 SGKDPNHFRPAGLPEKY (SEQ. ID. NO. 187)
GKDPNHFRPAGLPEKY (SEQ. ID. NO. 188)
KDPNHFRPAGLPEKY (SEQ. ID. NO. 189)
40 DPNHFRPAGLPEKY (SEQ. ID. NO. 190)
PNHFRPAGLPEKY (SEQ. ID. NO. 191)
45 NHFRPAGLPEKY (SEQ. ID. NO. 192)
HFRPAGLPEKY (SEQ. ID. NO. 193)
FRPAGLPEKY (SEQ. ID. NO. 194)
50 RPAGLPEKY (SEQ. ID. NO. 195)
PAGLPEKY (SEQ. ID. NO. 196)

AGLPEKY (SEQ. ID. NO. 197)

GLPEKY (SEQ. ID. NO. 198)

LPEKY (SEQ. ID. NO. 199)

PEKY (SEQ. ID. NO. 200)

EKY

Internal truncations of SAA include:

-RSF- and -RSF-5-105 wherein

5-105 means F, FS, FSF, ...

FLGEAFDGDARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 201)

-SFF- and -SFF-5-105 wherein

5-105 means S, SF, SFL, ...

GEAFDGDARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAA
EWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 202)

-FFS- and -FFS-5-105 wherein

5-105 means F, FL, FLG, ...

FLGEAFDGDARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 203)

-FSF- and -FSF-5-105 wherein

5-105 means L, LG, LGE, ...

FSFLGEAFDGDARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQ
AANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 204)

-SFL- and -SFL-5-105 wherein

5-105 means G, GE, GEA, ...

SFLGEAFDGDARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAA
ANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 205)

-FLG- and -FLG-5-105 wherein

5-105 means E, EA, EAF, ...

FLGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 206)

5

-LGE- and -LGE-5-105 wherein

5-105 means A, AF, AFD, ...

LGEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 207)

10

-GEA- and -GEA-5-105 wherein

5-105 means F, FD, FDG, ...

GEAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 208)

15

-EAF- and -EAF-5-105 wherein

5-105 means D, DG, DGA, ...

EAFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 209)

20

-AFD- and -AFD-5-105 wherein

5-105 means G, GA, GAR, ...

AFDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 210)

25

-FDG- and -FDG-5-105 wherein

5-105 means A, AR, ARD, ...

FDGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 211)

30

-DGA- and -DGA-5-105 wherein

5-105 means R, RD, RDM, ...

DGARMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEASNARENIQRRFFGRGAEDSLADQAA
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 212)

35

-GAR- and -GAR-5-105 wherein

5-105 means D, DM, DMW, ...

GARDMWRAYSMDREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 213)

5 -ARD- and -ARD-5-105 wherein

5-105 means M, MW, MWR, ...

ARDMWRAYSMDREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 214)

10 -RDM- and -RDM-5-105 wherein

5-105 means W, WR, WRA, ...

RDMWRAYSDMREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 215)

15 -DMW- and -DMW-5-105 wherein

5-105 means R, RA, RAY, ...

DMWRAYSDMREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 216)

20 -MWR- and -MWR-5-105 wherein

5-105 means A, AY, AYS, ...

MWRAYSDMREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 217)

25 -WRA- and -WRA-5-105 wherein

5-105 means Y, YS, YSD, ...

WRAYSDMREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 218)

30 -RAY- and -RAY-5-105 wherein

5-105 means S, SD, SDM, ...

RAYSDMREANYIGSDKYFHARGNYDAAKRPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 219)

35 -AYS- and -AYS-5-105 wherein

5-105 means D, DM, DMR, ...

AYSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFR
PAGLPEKY (SEQ. ID. NO. 220)

-YSD- and -YSD-5-105 wherein

5 5-105 means M, MR, MRE, ...

YSDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRP
AGLPEKY (SEQ. ID. NO. 221)

-SDM- and -SDM-5-105 wherein

10 5-105 means R, RE, REA, ...

SDMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPA
GLPEKY (SEQ. ID. NO. 222)

-DMR- and -DMR-5-105 wherein

15 5-105 means E, EA, EAN, ...

DMREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAG
LPEKY (SEQ. ID. NO. 223)

-MRE- and -MRE-5-105 wherein

20 5-105 means A, AN, ANY, ...

MREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGL
PEKY (SEQ. ID. NO. 224)

-REA- and -REA-5-105 wherein

25 5-105 means N, NY, NYI, ...

REANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGL
EKY (SEQ. ID. NO. 225)

-EAN- and -EAN-5-105 wherein

30 5-105 means Y, YI, YIG, ...

EANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGL
PEKY (SEQ. ID. NO. 226)

-ANY- and -ANY-5-105 wherein

35 5-105 means I, IG, IGS, ...

ANYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEK
Y (SEQ. ID. NO. 227)

-NYI- and -NYI-5-105 wherein

5 5-105 means G, GS, GSD, ...

NYIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 228)

-YIG- and -YIG-5-105 wherein

10 5-105 means S, SD, SDK, ...

YIGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 229)

-IGS- and -IGS-5-105 wherein

15 5-105 means D, DK, DKY, ...

IGSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 230)

-GSD- and -GSD-5-105 wherein

20 5-105 means K, KY, KYF, ...

GSDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY
(SEQ. ID. NO. 231)

-SDK- and -SDK-5-105 wherein

25 5-105 means Y, YF, YFH, ...

SDKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ.
ID. NO. 232)

-DKY- and -DKY-5-105 wherein

30 5-105 means F, FH, FHA, ...

DKYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ.
ID. NO. 233)

-KYF- and -KYF-5-105 wherein

35 5-105 means H, HA, HAR, ...

KYFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 234)

-YFH- and -YFH-5-105 wherein

5 5-105 means A, AR, ARG, ...
YFHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 235)

-FHA- and -FHA-5-105 wherein

10 5-105 means R, RG, RGN, ...
FHARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 236)

-HAR- and -HAR-5-105 wherein

15 5-105 means G, GN, GNY, ...
HARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 237)

-ARG- and -ARG-5-105 wherein

20 5-105 means N, NY, NYD, ...
ARGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 238)

-RGN- and -RGN-5-105 wherein

25 5-105 means Y, YD, YDA, ...
RGNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 239)

-GNY- and -GNY-5-105 wherein

30 5-105 means D, DA, DAA, ...
GNYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 240)

-NYD- and -NYD-5-105 wherein

35 5-105 means A, AA, AAK, ...
NYDAAKRGPGGVWAAEAISNARENIQRRFFGRGAEDSLADQAAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 241)

- 5 ·YDA- and -YDA-5-105 wherein
5-105 means A, AK, AKR, ...
YDAAKRGPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 242)
- 10 ·DAA- and -DAA-5-105 wherein
5-105 means K, KR, KRG, ...
DAAKRGPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 243)
- 15 ·AAK- and -AAK-5-105 wherein
5-105 means R, RG, RGP, ...
AAKRGPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 244)
- 20 ·AKR- and -AKR-5-105 wherein
5-105 means G, GP, GPG, ...
AKRGPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 245)
- 25 ·KRG- and -KRG-5-105 wherein
5-105 means P, PG, PGG, ...
KRGPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 245)
- 30 ·RGP- and -RGP-5-105 wherein
5-105 means G, GG, GGV, ...
RGPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 247)
- 35 ·GPG- and -GPG-5-105 wherein
5-105 means G, GV, GVW, ...
GPGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 248)
- 40 ·PGG- and -PGG-5-105 wherein
5-105 means V, VW, VWA, ...
PGGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 249)
- 45 ·GGV- and -GGV-5-105 wherein
5-105 means W, WA, WWA, ...
GGVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 250)

-GVW- and -GVW-5-105 wherein

5-105 means A, AA, AAE, ...

GVWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 251)

5

-VWA- and -VWA-5-105 wherein

5-105 means A, AE, AEA, ...

VWAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 252)

10

-WAA- and -WAA-5-105 wherein

5-105 means E, EA, EAI, ...

WAAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 253)

-AAE- and -AAE-5-105 wherein

15

5-105 means A, AI, AIS, ...

AAEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 254)

-AEA- and -AEA-5-105 wherein

5-105 means I, IS, ISN, ...

20

AEAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 255)

-EAI- and -EAI-5-105 wherein

5-105 means S, SN, SNA, ...

EAISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 256)

25

-AIS- and -AIS-5-105 wherein

5-105 means N, NA, NAR, ...

AISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 257)

30

-ISN- and -ISN-5-105 wherein

5-105 means A, AR, ARE, ...

ISNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 258)

-SNA- and -SNA-5-105 wherein

35

5-105 means R, RE, REN, ...

SNARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 259)

- 5 -NAR- and -NAR-5-105 wherein
5-105 means E, EN, ENI, ...
NARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 260)
- 10 -ARE- and -ARE-5-105 wherein
5-105 means N, NI, NIQ, ...
ARENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 261)
- 15 -REN- and -REN-5-105 wherein
5-105 means I, IQ, IQR, ...
RENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 262)
- 20 -ENI- and -ENI-5-105 wherein
5-105 means Q, QR, QRF, ...
ENIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 263)
- 25 -NIQ- and -NIQ-5-105 wherein
5-105 means R, RF, RFF, ...
NIQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 264)
- 30 -IQR- and -IQR-5-105 wherein
5-105 means F, FF, FFG, ...
IQRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 265)
- 35 -QRF- and -QRF-5-105 wherein
5-105 means G, GR, GRG, ...
QRFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 266)
- 40 -RFF- and -RFF-5-105 wherein
5-105 means R, RG, RGA, ...
RFFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 267)
- 45 -FFG- and -FFG-5-105 wherein
5-105 means R, RG, RGA, ...
FFGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 268)

- 5 ·FGR- and ·FGR-5-105 wherein
5-105 means G, GA, GAE, ...
FGRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 269)
- GRG- and ·GRG-5-105 wherein
5-105 means A, AE, AED, ...
GRGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 270)
- 10 ·RGA- and ·RGA-5-105 wherein
5-105 means E, ED, EDS, ...
RGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 271)
- GAE- and ·GAE-5-105 wherein
15 5-105 means D, DS, DSL, ...
GAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 272)
- AED- and ·AED-5-105 wherein
5-105 means S, SL, SLA, ...
20 AEDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 273)
- EDS- and ·EDS-5-105 wherein
5-105 means L, LA, LAD, ...
EDSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 274)
- 25 ·DSL- and ·DSL-5-105 wherein
5-105 means A, AD, ADQ, ...
DSLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 275)
- 30 ·SLA- and ·SLA-5-105 wherein
5-105 means D, DQ, DQA, ...
SLADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 276)
- 35 ·LAD- and ·LAD-5-105 wherein
5-105 means Q, QA, QAA, ...
LADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 277)

- 5 -ADQ- and -ADQ-5-105 wherein
5-105 means A, AA, AAN, ...
ADQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 278)
- 10 -DQA- and -DQA-5-105 wherein
5-105 means A, AN, ANE, ...
DQAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 279)
- 15 -QAA- and -QAA-5-105 wherein
5-105 means N, NE, NEW, ...
QAANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 280)
- 20 -AAN- and -AAN-5-105 wherein
5-105 means E, EW, EWG, ...
AANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 281)
- 25 -ANE- and -ANE-5-105 wherein
5-105 means W, WG, WGR, ...
ANEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 282)
- 30 -NEW- and -NEW-5-105 wherein
5-105 means G, GR, GRS, ...
NEWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 283)
- 35 -EWG- and -EWG-5-105 wherein
5-105 means R, RS, RSG, ...
EWGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 284)
- WGR- and -WGR-5-105 wherein
5-105 means S, SG, SGK, ...
WGRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 285)
- GRS- and -GRS-5-105 wherein
5-105 means G, GK, GKD, ...
GRSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 286)

- 5 -RSG- and -RSG-5-105 wherein
5-105 means K, KD, KDP, ...
RSGKDPNHFRPAGLPEKY (SEQ. ID. NO. 287)
- SGK- and -SGK-5-105 wherein
5-105 means D, DP, DPN, ...
SGKDPNHFRPAGLPEKY (SEQ. ID. NO. 288)
- 10 -GKD- and -GKD-5-105 wherein
5-105 means P, PN, PNH, ...
GKDPNHFRPAGLPEKY (SEQ. ID. NO. 289)
- KDP- and -KDP-5-105 wherein
15 5-105 means N, NH, NHF, ...
KDPNHFRPAGLPEKY (SEQ. ID. NO. 290)
- DPN- and -DPN-5-105 wherein
5-105 means H, HF, HFR, ...
20 DPNHFRPAGLPEKY (SEQ. ID. NO. 291)
- PNH- and -PNH-5-105 wherein
5-105 means F, FR, FRP, ...
PNHFRPAGLPEKY (SEQ. ID. NO. 292)
- 25 -NHF- and -NHF-5-105 wherein
5-105 means R, RP, RPA, ...
NHFPRAGLPEKY (SEQ. ID. NO. 293)
- 30 -HFR- and -HFR-5-105 wherein
5-105 means P, PA, PAG, ...
HFRPAGLPEKY (SEQ. ID. NO. 294)
- 35 -FRP- and -FRP-5-105 wherein
5-105 means A, AG, AGL, ...
FRPAGLPEKY (SEQ. ID. NO. 295)

- 5 -RPA- and -RPA-5-105 wherein
5-105 means G, GL, GLP, ...
RPAGLPEKY (SEQ. ID. NO. 296)
- 10 -PAG- and -PAG-5-105 wherein
5-105 means L, LP, LPE, ...
PAGLPEKY (SEQ. ID. NO. 297)
- 15 -AGL- and -AGL-5-105 wherein
5-105 means P, PE, PEK, ...
AGLPEKY (SEQ. ID. NO. 298)
- 20 -GLP- and -GLP-5-105 wherein
5-105 means E, EK, EKY, ...
GLPEKY (SEQ. ID. NO. 299)
- 25 -LPE- and -LEP-5-105 wherein
5-105 means K, KY
LPEKY (SEQ. ID. NO. 300)
- 30 -PEK- and -PEK-5-105 wherein
5-105 means Y, ...
PEKY (SEQ. ID. NO. 301)
- 35 -EKY-

30 The peptides described above are preferably analyzed in SAA/FPRL1 characterization assays to determine their effect on the assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. One of skill in the art will appreciate that carboxy truncations, amino truncations, and internal truncations of the FPRL1 protein can be made in a similar fashion and these molecules can be characterized in SAA/FPRL1 characterization assays.

35 In many embodiments, we use isolated or purified SAA, FPRL1, or fragments thereof. The term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally occurring protein present in a living cell is not isolated, but the same protein, separated from some or all of the coexisting materials in the natural system, is isolated. The

term "purified" does not require absolute purity; rather it is intended as a relative definition. For example, proteins are routinely purified to electrophoretic homogeneity, as detected by Coomassie staining, and are suitable in several assays despite having the presence of contaminants.

In the disclosure below, we teach the preparation of multimeric supports having peptide agents that interact with FPRL1 or SAA and thereby modulate a cellular response. These multimeric supports have many uses including, but not limited to, the manufacture of biotechnological tools and components for pharmaceuticals, therapeutic and prophylactic agents.

Preparation of multimeric supports and multimerized ligands

In order to be useful as a biotechnological tool or a component to a prophylactic or therapeutic agent, it is desirable to provide a peptide agent in such a form or in such a way that a sufficient affinity for FPRL1 or SAA is obtained. While a natural monomeric peptide agent (e.g., SAA and fragments thereof appearing as discrete units of the peptide each carrying only one binding epitope) is sufficient to interact with FPRL1 and thereby modulate a cellular response, synthetic ligands or multimeric ligands (e.g., SAA and fragments thereof appearing as multiple units of the peptide agent with several binding epitopes) can have far greater ability to interact with FPRL1 and thereby modulate a cellular response. It should be noted that the term "multimeric" is meant to refer to the presence of more than one unit of a ligand, for example several individual molecules of SAA or fragments thereof, as distinguished from the term "multimerized" which refers to the presence of more than one ligand joined as a single discrete unit, for example several molecules of SAA or fragments thereof joined in tandem.

A multimeric agent (synthetic or natural) that modulates a cellular response by effecting SAA/FPRL1 assembly or SAA/FPRL1-mediated signal transduction can be obtained by joining SAA or FPRL1, a fragment of SAA or FPRL1, or a peptidomimetic that resembles these molecules to a macromolecular support. A "support" can also be termed a carrier, a resin or any macromolecular structure used to attach or immobilize a peptide agent. Solid supports include, but are not limited to, the walls of wells of a reaction tray, test tubes, polystyrene beads, magnetic beads, nitrocellulose strips, membranes, microparticles such as latex particles, sheep (or other animal) red blood cells, artificial cells and others. The macromolecular support can have a hydrophobic surface that interacts with a portion of the peptide agent by hydrophobic non-covalent interaction. The hydrophobic surface of the support can also be a polymer such as plastic or any other polymer in which hydrophobic groups have been linked such as polystyrene, polyethylene or polyvinyl. Alternatively, the peptide agent can be covalently bound to carriers including proteins and oligo/polysaccharides (e.g. cellulose, starch, glycogen, chitosane or aminated sepharose). In these later embodiments, a reactive group on the peptide agent, such as a hydroxy or an amino group, can be used to join to a reactive group on the carrier so as to create the covalent bond. The support can also have a charged surface that interacts with the peptide agent. Additionally, the support can have other reactive groups which can be chemically activated so as to attach a peptide agent. For example, cyanogen bromide activated matrices, epoxy activated matrices, thio and

thiopropyl gels, nitrophenyl chloroformate and N-hydroxy succinimide chloroformate linkages, and oxirane acrylic supports are common in the art. (Sigma).

The support can also comprise an inorganic carrier such as silicon oxide material (e.g. silica gel, zeolite, diatomaceous earth or aminated glass) to which the peptide agent is covalently linked through a hydroxy, carboxy or amino group and a reactive group on the carrier. Furthermore, in some embodiments, a liposome or lipid bilayer (natural or synthetic) is contemplated as a support and peptide agents are attached to the membrane surface or are incorporated into the membrane by techniques in liposome engineering. By one approach, liposome multimeric supports comprise a peptide agent that is exposed on the surface of the bilayer and a second domain which anchors the peptide agent to the lipid bilayer. The anchor can be constructed of hydrophobic amino acid residues, resembling known transmembrane domains, or can comprise ceramides that are attached to the first domain by conventional techniques.

Carriers for use in the body, (i.e. for prophylactic or therapeutic applications) are desirably physiological, non-toxic and preferably, non-immunoresponsive. Suitable carriers for use in the body include poly-L-lysine, poly-D, L-alanine, liposomes, and Chromosorb® (Johns-Manville Products, Denver Co.). Ligand conjugated Chromosorb® (Synsorb-Pk) has been tested in humans for the prevention of hemolytic-uremic syndrome and was reported as not presenting adverse reactions. (*Armstrong et al. J. Infectious Diseases 171:1042-1045 (1995)*). For some embodiments, a "naked" carrier (i.e., lacking an attached peptide agent) that has the capacity to attach a peptide agent in the body of a subject is administered. By this approach, a "prodrug-type" therapy is envisioned in which the naked carrier is administered separately from the peptide agent and, once both are in the body of the subject, the carrier and the peptide agent are assembled into a multimeric complex.

The insertion of linkers, such as λ linkers, of an appropriate length between the peptide agent and the support are also contemplated so as to encourage greater flexibility of the peptide agent and thereby overcome any steric hindrance that can be presented by the support. The determination of an appropriate length of linker that allows for an optimal cellular response or lack thereof, can be determined by screening the peptide agents with varying linkers in the assays detailed in the present disclosure.

A composite support comprising more than one type of peptide agent is also envisioned. A "composite support" can be a carrier, a resin, or any macromolecular structure used to attach or immobilize two or more different peptide agents that modulate a cellular response by effecting SAA/FPRL1 assembly or SAA/FPRL1-mediated signal transduction. In some embodiments, a liposome or lipid bilayer (natural or synthetic) is contemplated for use in constructing a composite support and peptide agents are attached to the membrane surface or are incorporated into the membrane using techniques in liposome engineering.

As above, the insertion of linkers, such as λ linkers, of an appropriate length between the peptide agent and the support is also contemplated so as to encourage greater flexibility in the molecule and thereby overcome any steric hindrance that can occur. The determination of an appropriate length of linker that allows

for an optimal cellular response or lack thereof, can be determined by screening the ligands with varying linkers in the assays detailed in the present disclosure.

In other embodiments of the present invention, the multimeric and composite supports discussed above can have attached multimerized ligands so as to create a "multimerized-multimeric support" and a "multimerized-composite support", respectively. A multimerized ligand can, for example, be obtained by coupling two or more peptide agents in tandem using conventional techniques in molecular biology. The multimerized form of the ligand can be advantageous for many applications because of the ability to obtain an agent with a better ability modulate assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction and, thereby, effect a cellular response. We further contemplate that the incorporation of linkers or spacers, such as flexible λ linkers, between the individual domains that make-up the multimerized agent can be advantageous. The insertion of λ linkers of an appropriate length between protein binding domains, for example, can encourage greater flexibility in the molecule and can overcome steric hindrance. Similarly, the insertion of linkers between the multimerized ligand and the support can encourage greater flexibility and limit steric hindrance presented by the support. The determination of an appropriate length of linker that allows for an optimal effect on SAA/FPRL1 assembly or SAA/FPRL1-mediated signal transduction, can be determined by screening the ligands with varying linkers in the assays detailed in this disclosure.

In preferable embodiments, the various types of supports discussed above are created using SAA, FPRL1, a fragment of SAA or FPRL1, or a peptidomimetic that resembles these molecules. The multimeric supports, composite supports, multimerized-multimeric supports, or multimerized-composite supports, collectively referred to as "support-bound agents", are also preferably constructed using SAA, FPRL1, a fragment of SAA or FPRL1, or a peptidomimetic that resembles these molecules.

In the following section, we provide several assay methods, which are embodiments of the invention.

Methods to identify SAA/FPRL1 assembly and agents that modulate SAA/FPRL1 complex assembly

We have discovered that SAA efficiently associates with FPRL1 to form a SAA/FPRL1 complex. The association of SAA to FPRL1 can be measured using many techniques common to molecular biology. By one approach, assembly of the SAA/FPRL1 complex is analyzed by contacting a support having FPRL1 or a representative fragment thereof with SAA or a representative fragment of SAA. If the SAA or fragment thereof is detectably labeled (e.g., ^{125}I), the association to immobilized FPRL1 (or FPRL1 fragment) can be directly determined by detecting the signal (e.g., scintillation counting). Alternatively, the association of SAA or fragment thereof with FPRL1 can be determined indirectly by employing a detectably labeled antibody that has an epitope that corresponds to a region of SAA. In these assays, the support can be a resin, plastic, a membrane, a lipid, and a cell. Additionally, the SAA can be joined to a second support. Many SAA/FPRL1 characterization assays can be automated (e.g., high throughput screening employing a fluorescently labeled SAA or fragment of SAA) so as to quickly identify regions of the molecule that are involved in binding to FPRL1. Values or results from these assays can be recorded on a computer readable media (e.g., in a database)

and analyzed with a search program and retrieval program. Of course, embodiments of the invention include the converse of the assay described above. That is, immobilizing SAA or fragments thereof on a support and detecting the adhesion of labeled FPRL1 or fragments of FPRL1.

Additional embodiments include methods of identifying agents that modulate assembly of the SAA/FPRL1 complex. By one approach, an agent that modulates assembly of the SAA/FPRL1 complex can be identified by contacting a support having FPRL1 or a representative fragment thereof with SAA or a fragment of SAA in the presence of the agent. Detection of SAA dependent adhesion is accomplished, as described above, and successful agents are identified according to their ability to induce a desired modulation of the formation of the SAA-FPRL1 complex. As above, the support can be a resin, a membrane, plastic, a lipid, or a cell and the SAA can be joined to a second support. In another approach, a support having SAA or a representative fragment thereof can be used to capture directly or indirectly labeled FPRL1 or fragments of FPRL1. In some aspects, the fragments of SAA that are used have a polypeptide sequence that binds to FPRL1 and is at least 80% homologous to SAA. As above, binding is conducted in the presence of the agent and SAA dependent adhesion to FPRL1 is determined by the amount of labeled FPRL1 bound to the immobilized SAA. In this method, the support can be a resin, a membrane, plastic, a lipid, and a cell and the FPRL1 can also be joined to a second support to approximate native binding conditions.

In a preferred approach, an agent that modulates assembly of the SAA/FPRL1 complex is identified using a cell-based assay. Accordingly, cells are transfected with a construct comprising a nucleic acid sequence encoding FPRL1 or a representative fragment thereof that is involved in the assembly of the SAA/FPRL1 complex. Transfectants are brought in contact with labeled SAA or a fragment thereof and, as above, binding is conducted in the presence of the agent. SAA dependent adhesion to FPRL1 is determined by the amount of labeled SAA bound to the FPRL1 expressing cells. Additionally, a two-support adhesion assay can be employed in which a first cell that expresses FPRL1 and a second support having SAA are contacted in the presence of a peptide agent. Accordingly, the inhibition of aggregation of the two supports in the presence of the peptide agent indicates that the agent is effective at disrupting assembly of the SAA/FPRL1 complex.

In some aspects of the invention, nucleic acids encoding SAA, nucleic acids complementary to SAA, SAA protein, and polypeptide fragments of SAA are agents that modulate (e.g., inhibit or enhance) the formation of the SAA-FPRL1 complex. Several embodiments are provided that inhibit the association of SAA in a SAA/FPRL1 complex, for example, and thus, effect a cellular response. One embodiment of an SAA/FPRL1 inhibitory agent is an antisense oligonucleotide or ribozyme that hybridizes to nucleic acid encoding regions of SAA or FPRL1. By "antisense oligonucleotide" is meant a nucleic acid or modified nucleic acid including, but not limited to DNA, RNA, modified DNA or RNA (including branched chain nucleic acids and 2' O-methyl RNA) and PNA (polyamide nucleic acid).

Several ribozymes known to those of skill in the art can be easily designed to hybridize to nucleic acid sequence encoding SAA or FPRL1 and thereby inhibit the production of functional protein. Desirably, antisense oligonucleotides or ribozymes that hybridize to the start codon of SAA or FPRL1 are used. In one embodiment,

full length antisense *SAA* is used to significantly reduced assembly of the SAA/FPRL1 complex. Many other antisense oligonucleotides or ribozymes that interfere with the assembly of the SAA/FPRL1 complex can be designed and screened by the methods detailed previously.

5 The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., *Ann. Rev. Biochem.*, 55:569-597 (1986) and Izant and Weintraub, *Cell*, 36:1007-1015 (1984). In some strategies, antisense molecules are obtained from a nucleotide sequence encoding SAA or FPRL1 by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. Antisense molecules and ribozymes can be prepared by any method known in the art for the synthesis of RNA molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis.

15 Additionally, RNA molecules can be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding SAA or FPRL1. Such DNA sequences can be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Further, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly can be introduced into cell lines, cells or tissues. Still further, oligonucleotides that are complementary to the mRNA encoding SAA or FPRL1 can be synthesized *in vitro*. Thus, antisense nucleic acids are capable of hybridizing to *SAA or FPRL1* mRNA to create a duplex. In some embodiments, the antisense sequences can contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine and wybutosine as well as acetyl-, methyl-, thio- and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine that are not as easily recognized by endogenous endonucleases. Further examples are described by Rossi et al., *Pharmacol. Ther.*, 50(2):245-254, (1991).

20 Various types of antisense oligonucleotides complementary to the *SAA or FPRL1* mRNA can be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT WO94/23026, hereby incorporated by reference, are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides. In another preferred embodiment, the antisense oligodeoxynucleotides described in International Application No. WO 95/04141 are used. In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the

other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 can also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence that binds to control proteins and are effective as decoys therefor. These molecules can contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures. In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor. Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732, hereby incorporated by reference, is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides can be multifunctional, interacting with several regions that are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit assembly of the SAA/FPRL1 complex can be determined using *in vitro* expression analysis and the SAA/FPRL1 characterization assays described herein. The antisense molecule can be introduced into the cells expressing SAA or FPRL1 by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector can be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors can be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between $1 \times 10^{-10} \text{M}$ to $1 \times 10^{-4} \text{M}$. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of 1×10^{-7} translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher can be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from a vertebrate, such as a mammal or human, are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

Ribozymes can also be used to reduce or eliminate SAA or FPRL1 expression. Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Within the scope of aspects of the invention, are engineered hammerhead motif ribozyme molecules that can specifically and efficiently catalyze endonucleolytic cleavage of

a sequence encoding SAA or FPRL1, for example. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites that include the following sequences, GUA, GUU and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides corresponding to the region of the target gene containing the cleavage site can be evaluated for secondary structural features that can render the oligonucleotide inoperable. The suitability of candidate targets can also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays. Delivery of antisense and ribozyme agents by transfection and by liposome are quite well known in the art.

Another embodiment of an SAA/FPRL1 inhibitory agent is a polypeptide that interferes with the assembly of the SAA/FPRL1 complex. Polypeptide fragments that inhibit the assembly of the SAA/FPRL1 complex can be rapidly engineered and identified given the present disclosure and candidate polypeptides can contain regions of FPRL1 or SAA. The screening of polypeptide fragments and mutant proteins that inhibit assembly of the SAA/FPRL1 complex would be routine given the present disclosure and assays described herein. For example, polypeptide inhibitory agents can be identified by their ability to disrupt assembly of the SAA/FPRL1 complex by employing conventional affinity chromatography techniques, sandwich assays, ELISA assays, or other binding assays known to those of skill in the art and described above.

In another embodiment, concentrations of FPRL1 or SAA are raised in a cell so as to enhance assembly of the SAA/FPRL1 complex. There can be many ways to raise the concentration of FPRL1 or SAA in a cell. Liposome-mediated transfer, is one approach to deliver FPRL1 or SAA to a cell. Alternatively, the concentration of FPRL1 or SAA can be raised in a cell by transfecting constructs encoding these molecules. A construct for use in the transfection of FPRL1 into cells in culture is described and many others can be developed by those of skill in the art. Retroviral constructs for the delivery of nucleic acid encoding FPRL1 or SAA or fragments thereof or complements thereof are also contemplated and many retroviral vectors can be engineered accordingly. Other embodiments of inhibitory or enhancing agents (collectively referred to as "modulators") include antibodies, peptidomimetics, and chemicals that inhibit or enhance assembly of the SAA/FPRL1 complex. Several other methods for identifying agents that modulate are discussed below.

In the discussion that follows, we describe several methods of molecular modeling and rational drug design for the identification of ligands that resemble SAA and interact with FPRL1 or vice versa to effect cellular responses including, but not limited to, signal transduction, chemotaxis, leukocyte migration, immune system response, amyloidosis, inflammatory response, infection, organ rejection, arthritis, atherosclerosis, and neoplasia.

Methods of Rational Drug Design

Rational drug design involving polypeptides requires identifying and defining a first peptide with which the designed drug is to interact, and using the first target peptide to define the requirements for a second peptide. With such requirements defined, one can find or prepare an appropriate peptide or non-peptide

ligand that meets all or substantially all of the defined requirements. Thus, one goal of rational drug design is to produce structural or functional analogs of biologically active polypeptides of interest or of small molecules with which they interact (e.g., agonists, antagonists, null compounds) in order to fashion drugs that are, for example, more or less potent forms of the ligand. (See, e.g., Hodgson, *Bio. Technology* 9:19-21 (1991)). An example of rational drug design is the development of HIV protease inhibitors. (Erickson et al., *Science* 249:527-533 (1990)). Combinatorial chemistry is the science of synthesizing and testing compounds for bioactivity *en masse*, instead of one by one, the aim being to discover drugs and materials more quickly and inexpensively than was formerly possible. Rational drug design and combinatorial chemistry have become more intimately related in recent years due to the development of approaches in computer-aided protein modeling and drug discovery. See e.g., US Pat. No. 4,908,773; 5,884,230; 5,873,052; 5,331,573; and 5,888,738.

The use of molecular modeling as a combinatorial chemistry tool has dramatically increased due to the advent of computer graphics. Not only is it possible to view molecules on computer screens in three dimensions but it is also possible to examine the interactions of ligands with various macromolecules such as enzymes and receptors and rationally design derivative molecules to test. (See Boorman, *Chem. Eng. News* 70:18-26 (1992)). A vast amount of user-friendly software and hardware is now available and virtually all pharmaceutical companies have computer modeling groups devoted to rational drug design. Molecular Simulations Inc., for example, (www.msi.com) sells several sophisticated programs that allow a user to start from an amino acid sequence, build a two or three-dimensional model of the protein or polypeptide, compare it to other two and three-dimensional models, and analyze the interactions of compounds, drugs, and peptides with a three dimensional model in real time.

Accordingly, in some embodiments of the invention, software is used to compare regions of SAA or FPRL1 and fragments thereof that are involved in the assembly of the SAA/FPRL1 complex with other molecules, such as peptides, peptidomimetics, and chemicals, so that therapeutic interactions of new molecules (e.g., ligands for FPRL1) can be predicted and new derivative molecules can be designed. (Schneider, *Genetic Engineering News* December: page 20 (1998), Tempczyk et al., *Molecular Simulations Inc. Solutions* April (1997) and Butenhof, *Molecular Simulations Inc. Case Notes* (August 1998)). Libraries of molecules that resemble SAA or FPRL1 or that effect assembly of the SAA/FPRL1 complex and, thereby inhibit or enhance the function of FPRL1 (e.g., "modulate" FPRL1 induced cellular response) can be created. In some contexts, the term "FPRL1 modulating agent" or "modulators" includes SAA or FPRL1, polypeptide fragments corresponding to SAA or FPRL1, fusion proteins comprising SAA or FPRL1 or polypeptide fragments of these molecules, nucleic acids encoding these molecules, as well as, peptidomimetics, chemicals, and other molecules that modulate assembly of the SAA/FPRL1 complex.

As a starting point to rational drug design, a two or three dimensional model of a polypeptide of interest is created (e.g., SAA, FPRL1, and/or fragments thereof). In the past, the three-dimensional structure of proteins has been determined in a number of ways. Perhaps the best known way of determining protein structure involves the use of x-ray crystallography. A general review of this technique can be found in Van Holde, K.E. *Physical Biochemistry*, Prentice-Hall, N.J. pp. 221-239 (1971). Using this technique, it is possible to elucidate three-

dimensional structure with good precision. Additionally, protein structure can be determined through the use of techniques of neutron diffraction, or by nuclear magnetic resonance (NMR). (See, e.g., Moore, W.J., *Physical Chemistry*, 4th Edition, Prentice-Hall, N.J. (1972)).

Alternatively, the protein model embodiments of the present invention can be constructed using computer-based protein modeling techniques. By one approach, the protein folding problem is solved by finding target sequences that are most compatible with profiles representing the structural environments of the residues in known three-dimensional protein structures. (See, e.g., U.S. Patent No. 5,436,850). In another technique, the known three-dimensional structures of proteins in a given family are superimposed to define the structurally conserved regions in that family. This protein modeling technique also uses the known three-dimensional structure of a homologous protein to approximate the structure of a polypeptide of interest. (See e.g., U.S. Patent Nos. 5,557,535; 5,884,230; and 5,873,052). Conventional homology modeling techniques have been used routinely to build models of proteases and antibodies. (Sowdhamini et al., *Protein Engineering* 10:207, 215 (1997)). Comparative approaches can also be used to develop three-dimensional protein models when the protein of interest has poor sequence identity to template proteins. In some cases, proteins fold into similar three-dimensional structures despite having very weak sequence identities. For example, the three-dimensional structures of a number of helical cytokines fold in similar three-dimensional topology in spite of weak sequence homology.

The recent development of threading methods and "fuzzy" approaches now enables the identification of likely folding patterns and functional protein domains in a number of situations where the structural relatedness between target and template(s) is not detectable at the sequence level. By one method, fold recognition is performed using Multiple Sequence Threading (MST) and structural equivalences are deduced from the threading output using the distance geometry program DRAGON that constructs a low resolution model. A full-atom representation is then constructed using a molecular modeling package such as QUANTA.

According to this 3-step approach, candidate templates are first identified by using the novel fold recognition algorithm MST, which is capable of performing simultaneous threading of multiple aligned sequences onto one or more 3-D structures. In a second step, the structural equivalences obtained from the MST output are converted into interresidue distance restraints and fed into the distance geometry program DRAGON, together with auxiliary information obtained from secondary structure predictions. The program combines the restraints in an unbiased manner and rapidly generates a large number of low resolution model confirmations. In a third step, these low resolution model confirmations are converted into full-atom models and subjected to energy minimization using the molecular modeling package QUANTA. (See e.g., Aszódi et al., *Proteins: Structure, Function, and Genetics*, Supplement 1:38-42 (1997)).

In a preferred approach, the commercially available "Insight II 98" program (Molecular Simulations Inc.) and accompanying modules are used to create a two and/or three dimensional model of a polypeptide of interest (e.g., SAA or FPRL1 or a fragment thereof) from an amino acid sequence. Insight II is a three-dimensional graphics program that can interface with several modules that perform numerous structural analysis and enable real-time

rational drug design and combinatorial chemistry. Modules such as Builder, Biopolymer, Consensus, and Converter, for example, allow one to rapidly create a two dimensional or three dimensional model of a polypeptide, carbohydrate, nucleic acid, chemical or combinations of the foregoing from their sequence or structure. The modeling tools associated with Insight II support many different data file formats including Brookhaven and Cambridge databases; AMPAC/MOPAC and QCPE programs; Molecular Design Limited Molfile and SD files, Sybel Mol2 files, VRML, and Pict files.

Additionally, the techniques described above can be supplemented with techniques in molecular biology to design models of the protein of interest. For example, a peptide of interest (e.g., FPRL1, SAA and/or fragments thereof) can be analyzed by an alanine scan (Wells, Methods in Enzymol. 202:390-411 (1991)) or other types of site-directed mutagenesis analysis. In alanine scan, each amino acid residue of the polypeptide of interest is sequentially replaced by alanine in a step-wise fashion (i.e., only one alanine point mutation is incorporated per molecule starting at position #1 and proceeding through the entire molecule), and the effect of the mutation on the peptide's activity in a SAA/FPRL1 characterization assay is determined. Each of the amino acid residues of the peptide is analyzed in this manner and the regions important for assembly of the SAA/FPRL1 complex are identified. These functionally important regions can be recorded on a computer readable medium, stored in a database in a computer system, and a search program can be employed to generate a protein model of the functionally important regions.

Once a model of the polypeptide of interest (e.g., SAA, FPRL1, or a fragment thereof) is created, it can be compared to other models so as to identify new agents ("candidate agents") that can effect assembly of the SAA/FPRL1 complex. By starting with the amino acid sequence or protein model, for example, ligands having two-dimensional and/or three-dimensional homology can be rapidly identified. In one approach, a percent sequence identity can be determined by standard methods that are commonly used to compare the similarity and position of the amino acid of two polypeptides. Using a computer program such as BLAST or FASTA, two polypeptides can be aligned for optimal matching of their respective amino acids (either along the full length of one or both sequences, or along a predetermined portion of one or both sequences). Such programs provide "default" opening penalty and a "default" gap penalty, and a scoring matrix such as PAM 250 (a standard scoring matrix; see Dayhoff et al., in: Atlas of Protein Sequence and Structure, Vol. 5, Supp. 3 (1978)) can be used in conjunction with the computer program. The percent identity can then be calculated as:

$$\frac{\text{total number of identical matches}}{[\text{length of the longer sequence within the matched span} + \text{number of gaps introduced into the longer sequence in order to align the two sequences}]} \times 100$$

Accordingly, the protein sequence corresponding to SAA or FPRL1 or fragments thereof can be compared to known sequences on a protein basis. Protein sequences corresponding to SAA and FPRL1 are compared, for example, to known amino acid sequences found in Swissprot release 35, PIR release 53 and

Genpept release 108 public databases using BLASTP with the parameter W=8 and allowing a maximum of 10 matches. In addition, the protein sequences encoding SAA are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001. The candidate ligands desirably have at least 50% homology and preferably have 60% or 70% or 80% or 90% or greater homology to SAA or FPRL1.

The candidate ligands can have the following degrees of homology to SAA or FPRL1, for example: 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, and 99%. The candidate ligands having greater than or equal to 50% homology are identified and are subsequently examined using the SAA/FPRL1 characterization assays described herein. Candidate ligands that can effect assembly of the SAA/FPRL1 complex and/or modulate SAA/FPRL1-mediated signal transduction are, thus, identified.

In another embodiment, computer modeling and the sequence-to-structure-to-function paradigm is exploited to identify more FPRL1 modulating agents that effect assembly of the SAA/FPRL1 complex and/or modulate SAA/FPRL1-mediated signal transduction. By this approach, first the structure of a modulator (e.g., SAA, FPRL1, or a fragment thereof) having a known response in a SAA/FPRL1 characterization assay is determined from its sequence using a threading algorithm, which aligns the sequence to the best matching structure in a structural database. Next, the protein's active site (i.e., the site important for a desired response in the characterization assay) is identified and a "fuzzy functional form" (FFF) -- a three-dimensional descriptor of the active site of a protein -- is created. (See e.g., Fetrow et al., *J. Mol. Biol.* 282:703-711 (1998) and Fetrow and Skolnick, *J. Mol. Biol.* 281: 949-968 (1998).

The FFFs are built by iteratively superimposing the protein geometries from a series of functionally related proteins with known structures. The FFFs are not overly specific, however, and the degree to which the descriptors can be relaxed is explored. In essence, conserved and functionally important residues for a desired response are identified and a set of geometric and conformational constraints for a specific function are defined in the form of a computer algorithm. The program then searches experimentally determined protein structures from a protein structural database for sets of residues that satisfy the specified constraints. In this manner, homologous three-dimensional structures can be compared and degrees (e.g., percentages of three-dimensional homology) can be ascertained. The ability to search three-dimensional structure databases for structural similarity to a protein of interest can also be accomplished by employing the Insight II using modules such as Biopolymer, Binding Site Analysis, and Profiles-3D.

By using this computational protocol, genome sequence data bases such as maintained by various organizations including: <http://www.tigr.org/tdb>; <http://www.genetics.wisc.edu>; <http://genome-www.stanford.edu/~ball>; <http://hiv-web.lanl.gov>; <http://www.ncbi.nlm.nih.gov>; <http://www.ebi.ac.uk>; <http://pasteur.fr/other/biology>; and <http://www-genome.wi.mit.edu>, can be rapidly screened for specific protein active sites and for identification of the residues at those active sites that resemble a desired molecule. Several other groups have developed databases of short sequence patterns or motifs designed to identify a

given function or activity of a protein. Many of these databases, notably Prosite (<http://expasy.hcuge.ch/sprot/prosite.html>); Blocks (<http://www.blocks.fhcrc.org>); Prints (<http://www.biochem.ucl.ac.uk/bsm/dbbrowser/PRINTS/PRINTS.html>), the Molecular Modelling Database (MMDB), and the Protein Data Bank can use short stretches of sequence information to identify sequence patterns that are specific for a given function; thus they avoid the problems arising from the necessity of matching entire sequences. In this manner, new modulating agents are rationally selected for further identification by SAA/FPRL1 characterization assays, as described above. Rounds or cycles of functional assays on the molecules and derivatives thereof and further FFF refinement and database searching allows an investigator to more narrowly define classes of modulating agents that produce a desired effect on assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction.

In addition to identifying naturally occurring ligands for SAA and/or FPRL1 or fragments thereof, a three-dimensional structure of these peptides can facilitate the design of derivative molecules that produce a more desirable cellular response. Polypeptide derivatives of the invention can be fragments of SAA or FPRL1 or homologs or mutants of SAA or FPRL1, or polypeptide fusions, modified polypeptides, peptidomimetics, or chemicals. For example, a derivative polypeptide can include a polypeptide that has been engineered to have one or more cystine residues incorporated into the protein so as to promote the formation of a more stable derivative through disulfide bond formation. (*See e.g.*, US Pat. No. 4,908,773). In the past, investigators have employed computers and computer graphics programs to aid in assessing the appropriateness of potential cystine linkage sites. (Perry, L. J., & Wetzel, R., *Science*, 226:555-557 (1984); Pabo, C. O., et al., *Biochemistry*, 25:5987-5991 (1986); Bott, R., et al., European Patent Application Ser. No. 130,756; Perry, L. J., & Wetzel, R., *Biochemistry*, 25:733-739 (1986); Wetzel, R. B., European Patent Application Ser. No. 155,832). The introduction of a cystine residue in a polypeptide can be accomplished using conventional molecular biology.

Additional polypeptide derivatives include peptidomimetics that resemble a polypeptide of interest. The naturally occurring amino acids employed in the biological production of peptides all have the L-configuration. Synthetic peptides can be prepared employing conventional synthetic methods, utilizing L-amino acids, D-amino acids, or various combinations of amino acids of the two different configurations. Synthetic compounds that mimic the conformation and desirable features of a particular peptide, e.g., an oligopeptide, once such peptide has been found, but that avoids the undesirable features, e.g., flexibility (loss of conformation) and bond breakdown are known as a "peptidomimetics". (*See, e.g.*, Spatola, A. F. *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins* (Weistein, B, Ed.), Vol. 7, pp. 267-357, Marcel Dekker, New York (1983), which describes the use of the methylenethio bioisostere [CH_2S] as an amide replacement in enkephalin analogues; and Szelke et al., *In peptides: Structure and Function, Proceedings of the Eighth American Peptide Symposium*, (Hruby and Rich, Eds.); pp. 579-582, Pierce Chemical Co., Rockford, Ill. (1983), which describes renin inhibitors having both the methyleneamino [CH_2NH] and hydroxyethylene [CHOHCH_2] bioisosteres at the Leu-Val amide bond in the 6-13 octapeptide derived from angiotensinogen).

In general, the designing and synthesizing of a peptidomimetic involves starting with the sequence of the peptide and the conformation data (e.g., geometry data, such as bond lengths and angles) of a desired peptide (e.g., the most probable simulated peptide), and using such data to determine the geometries that should be designed into the peptidomimetic. Numerous methods and techniques are known in the art for performing this step, any of which could be used. (*See, e.g.*, Farmer, P. S., Drug Design, (Ariens, E. J. ed.), Vol. 10, pp. 119-143 (Academic Press, New York, London, Toronto, Sydney and San Francisco) (1980); Farmer, et al., in TIPS, 9/82, pp. 362-365; Verber et al., in TINS, 9/85, pp. 392-396; Kaltenbronn et al., in J. Med. Chem. 33: 838-845 (1990); and Spatola, A. F., in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Vol. 7, pp. 267-357, Chapter 5, "Peptide Backbone Modifications: A Structure-Activity Analysis of Peptides Containing Amide Bond Surrogates. Conformational Constraints, and Relations" (B. Weisten, ed.; Marcell Dekker: New York, pub.) (1983); Kemp, D. S., "Peptidomimetics and the Template Approach to Nucleation of .beta.-sheets and .alpha.-helices in Peptides," Tibeck, Vol. 8, pp. 249-255 (1990). Additional teachings can be found in U.S. Patent Nos. 5,288,707; 5,552,534; 5,811,515; 5,817,626; 5,817,879; 5,821,231; and 5,874,529.

Once protein models of the functionally important regions of SAA and/or FPRL1 have been generated, a database comprising one or more libraries having peptides, chemicals, peptidomimetics and other agents can also be accessed by a search program and selected agents can be compared to the protein models to identify molecules that effect the assembly of the SAA/FPRL1 complex and/or modulate SAA/FPRL1-mediated signal transduction. Desirably, agents identified by the approach above are then tested in the SAA/FPRL1 characterization assays and are used to construct multimeric agents and/or are incorporated into pharmaceuticals. One program that allows for such analysis is Insight II having the Ludi module. Further, the Ludi/ACD module allows a user access to over 65,000 commercially available drug candidates (MDL's Available Chemicals Directory) and provides the ability to screen these compounds for interactions with the protein of interest.

By a similar approach, a modulating agent that interacts with FPRL1 or SAA can be manufactured and identified as follows. First, a molecular model of one or more modulating agents or portions of these molecules that interact with FPRL1 or SAA are created using one of the techniques discussed above or as known in the art. Next, chemical libraries and databases are searched for molecules similar in structure to the known FPRL1 modulating agents. That is, a search can be made of a three dimensional data base for non-peptide (organic) structures (e.g., non-peptide analogs, and/or dipeptide analogs) having three dimensional similarity to the known structure of the target compound. See, e.g., the Cambridge Crystal Structure Data Base, Crystallographic Data Center, Lensfield Road, Cambridge, CB2 1EW, England; and Allen, F. H., et al., Acta Crystallogr., B35: 2331-2339 (1979).

It is noted that search algorithms for three dimensional data base comparisons are available in the literature. See, e.g., Cooper, et al., J. Comput.-Aided Mol. Design, 3: 253-259 (1989) and references cited therein; Brent, et al., J. Comput.-Aided Mol. Design, 2: 311-310 (1988) and references cited therein.

Commercial software for such searches is also available from vendors such as Day Light Information Systems, Inc., Irvine, Calif. 92714, and Molecular Design Limited, 2132 Faralton Drive, San Leandro, Calif. 94577. The searching is done in a systematic fashion by simulating or synthesizing analogs having a substitute moiety at every residue level. Preferably, care is taken that replacement of portions of the backbone does not disturb the tertiary structure and that the side chain substitutions are compatible to retain the receptor substrate interactions.

Once candidate agents have been identified, desirably, they are analyzed in a SAA/FPRL1 characterization assay. The assays, described herein and assays that evaluate the formation of a SAA/FPRL1 complex in the presence of modulators, as will be apparent to one of skill in the art given the disclosure herein (referred to collectively as "FPRL1 characterization assays"), can be performed on the candidate agents and groups of modulating agents (wherein the grouping is based on the potency of modulation of the formation of a SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction) are identified and recorded on a computer readable media. Further cycles of modeling and SAA/FPRL1 characterization assays can be employed to more narrowly define the parameters needed in an optimal FPRL1 modulating agent.

Each FPRL1 modulating agent and its response in a FPRL1 characterization assay can be recorded on a computer readable media and a database or library of FPRL1 modulating agents and respective responses in the SAA/FPRL1 characterization assay can be generated. These databases or libraries can be used by researchers to identify important differences between active and inactive molecules so that compound libraries are enriched for modulating agents that have favorable characteristics. Further, enrichment can be achieved by using approaches in dynamic combinatorial chemistry. (See e.g., Angnew, *Chem. Int. Ed.*, 37:2828 (1998)). For example, a target biomolecule, such as FPRL1 or SAA, is joined to a support and is bound by the modulating agents from the libraries generated above. The FPRL1 resin bound with one or more candidate modulating agents is removed from the binding reaction, the modulating agents are eluted from the support, and are identified. Cycles of immobilized target binding assays are conducted, classes of modulating agents that exhibit desired binding characteristics are identified, and this data is recorded on a computer readable media and is used to select more modulating agents that produce a desired modulation of the formation of a SAA/FPRL1 complex and or SAA/FPRL1-mediated signal transduction.

Additionally, agents identified by the approaches described above can be synthesized on solid support beads by split-and-pool synthesis, a multistage process for producing very large numbers of compounds, to facilitate testing. The support-bound agents can be screened in SAA/FPRL1 characterization assays or "free mixtures" are created by cleaving the agent from the support and these free mixtures are screened in the FPRL1 characterization assays. Compounds that produce desirable responses are identified, recorded on a computer readable media, and the process can be repeated to select optimal FPRL1 modulating agents.

Many computer programs and databases can be used with embodiments of the invention to identify agents that modulate assembly of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction. The following list is intended not to limit the invention but to provide guidance to programs and databases that are

useful with the approaches discussed above. The programs and databases that can be used include, but are not limited to: MacPattern (EMBL), DiscoveryBase (Molecular Applications Group), GeneMine (Molecular Applications Group), Look (Molecular Applications Group), MacLook (Molecular Applications Group), BLAST and BLAST2 (NCBI), BLASTN and BLASTX (Altschul et al, *J. Mol. Biol.* 215: 403 (1990), herein incorporated by reference), FASTA (Pearson and Lipman, *Proc. Natl. Acad. Sci. USA*, 85: 2444 (1988), herein incorporated by reference), Catalyst (Molecular Simulations Inc.), Catalyst/SHAPE (Molecular Simulations Inc.), Cerius².DBAccess (Molecular Simulations Inc.), HypoGen (Molecular Simulations Inc.), Insight II, (Molecular Simulations Inc.), Discover (Molecular Simulations Inc.), CHARMM (Molecular Simulations Inc.), Felix (Molecular Simulations Inc.), DelPhi, (Molecular Simulations Inc.), QuanteMM, (Molecular Simulations Inc.), Homology (Molecular Simulations Inc.), Modeler (Molecular Simulations Inc.), Modeller 4 (Sali and Blundell *J. Mol. Biol.* 234:217-241 (1997)), ISIS (Molecular Simulations Inc.), Quanta/Protein Design (Molecular Simulations Inc.), WebLab (Molecular Simulations Inc.), WebLab Diversity Explorer (Molecular Simulations Inc.), Gene Explorer (Molecular Simulations Inc.), SeqFold (Molecular Simulations Inc.), the EMBL/Swissprotein database, the MDL Available Chemicals Directory database, the MDL Drug Data Report data base, the Comprehensive Medicinal Chemistry database, Derwent's World Drug Index database, and the BioByteMasterFile database. Many other programs and data bases would be apparent to one of skill in the art given the present disclosure.

In the discussion below, we describe several embodiments of the invention that have therapeutic and/or prophylactic application.

Therapeutic and prophylactic applications

In the therapeutic and prophylactic embodiments, the peptide agents identified as modulating the formation of the SAA/FPRL1 complex and/or SAA/FPRL1-mediated signal transduction are incorporated into a pharmaceutical product and are administered to a subject in need. The monomeric and multimeric peptide agents of the invention are suitable for treatment of subjects either as a preventive measure to avoid a particular cellular response or as a therapeutic to treat subjects in need of a particular cellular response.

One contemplated method of making a pharmaceutical involves the selection of a peptide agent that interacts with FPRL1, preferably SAA, a fragment of SAA, or a peptidomimetic that resembles SAA or a fragment thereof, and incorporating the peptide agent into a pharmaceutical by conventional techniques. Additionally, a peptide agent such as FPRL1, a fragment of FPRL1, or a peptidomimetic that resembles FPRL1 or a fragment thereof can be incorporated into a pharmaceutical. The pharmaceuticals of the present invention can be formulated with an adjuvant or can be free and desirable embodiments provide the peptide agent in a support-bound form. Optionally, the peptide agent can be provided in an aggregated form as created, for example, by heating.

In another method of making a pharmaceutical, we envision incorporating a peptide agent selected for its ability to block, inhibit, or prevent a cellular response in the characterization assays described above. Accordingly, a peptide agent that interacts with FPRL1 or SAA and blocks, inhibits, or suspends a cellular response by effecting the assembly of the SAA/FPRL1 complex is identified and is incorporated into a pharmaceutical by conventional

techniques. A novel class of peptide agents that bind FPRL1 or SAA with high avidity but fail to induce a cellular response can be designed using approaches described above. These pharmaceuticals are formulated in adjuvant or free and are provided in the form of a support-bound agent, as well. As above, an aggregated form of this embodiment can be created by heating the proteins and can administered to subjects in need.

5 The compounds of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral) or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylose or starch, magnesium
10 stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. They can
15 also be combined where desired with other active agents, e.g., vitamins. The ligands can also be administered in the form of a support-bound agent or in a pro-drug form which interacts with a support so as to create a support-bound agent in the body of the subject. Further, the manufacture of pharmaceuticals or therapeutic agents that deliver the peptide agent and/or a nucleic acid sequence encoding the peptide agent by several routes is another aspect of the invention. For example, and not by way of limitation, the use of DNA, RNA, and
20 viral vectors having sequence encoding the peptide agent is contemplated. Nucleic acids encoding a desired peptide agent can be administered alone or in combination with peptide agents.

In the following disclosure, doses and methods of administration are provided.

Dosage and methods of administration

25 The effective dose and method of administration of a particular formulation of a peptide agent can vary based on the individual subject and the stage of the disease, as well as other factors known to those of skill in the art. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio of
30 toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the
35 patient, and the route of administration.

The exact dosage is chosen by the individual physician in view of the patient to be treated. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Additional factors which can be taken into account include the severity of the disease state, age, weight and gender of the patient; diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long acting pharmaceutical compositions might be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

Normal dosage amounts can vary from 0.1 to 100,000 micrograms, up to a total dose of about 10 grams, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature. (See U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212.) More specifically, the dosage of the peptide agents of the present invention is one that provides sufficient peptide agent to attain a desirable effect including an up-regulation or a down regulation of a cellular response. A constant infusion of the peptide agent can also be provided so as to maintain a stable concentration in the tissues as measured by blood levels.

Routes of administration of the peptide agents include, but are not limited to, topical, transdermal, parenteral, gastrointestinal, transbronchial, and transalveolar. Topical administration is accomplished via a topically applied cream, gel, rinse, etc. containing a peptide agent. Transdermal administration is accomplished by application of a cream, rinse, gel, etc. capable of allowing the peptide agent to penetrate the skin and enter the blood stream. Parenteral routes of administration include, but are not limited to, electrical or direct injection such as direct injection into a central venous line, intravenous, intramuscular, intraperitoneal or subcutaneous injection. Gastrointestinal routes of administration include, but are not limited to, ingestion and rectal. Transbronchial and transalveolar routes of administration include, but are not limited to, inhalation, either via the mouth or intranasally.

Compositions of peptide agent-containing compounds suitable for topical application include, but not limited to, physiologically acceptable implants, ointments, creams, rinses, and gels. Any liquid, gel, or solid, pharmaceutically acceptable base in which the peptide agents are at least minimally soluble is suitable for topical use in aspects of the present invention. For topical application, there are also employed as non-sprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a freon.

Compositions of the peptide agents suitable for transdermal administration include, but are not limited to, pharmaceutically acceptable suspensions, oils, creams, and ointments applied directly to the skin or incorporated into a protective carrier such as a transdermal device ("transdermal patch"). Examples of suitable creams, ointments, etc. can be found, for instance, in the Physician's Desk Reference. Examples of suitable transdermal devices are described, for instance, in U.S. Patent No. 4,818,540 issued April 4, 1989 to Chinen, et al.

Compositions of the peptide agents suitable for parenteral administration include, but are not limited to, pharmaceutically acceptable sterile isotonic solutions. Such solutions include, but are not limited to, saline and phosphate buffered saline for injection into a central venous line, intravenous, intramuscular, intraperitoneal, or subcutaneous injection of the peptides. Additional embodiments for parenteral application include injectable, sterile, oily solutions, suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

Compositions of the peptide agents suitable for transbronchial and transalveolar administration include, but not limited to, various types of aerosols for inhalation. Devices suitable for transbronchial and transalveolar administration of the peptide agents are also embodiments. Such devices include, but are not limited to, atomizers and vaporizers. Many forms of currently available atomizers and vaporizers can be readily adapted to deliver peptide agents.

Compositions of the peptide agents suitable for gastrointestinal administration include, but not limited to, pharmaceutically acceptable powders, tablets, pills, dragees, capsules, drops, or liquids for ingestion and suppositories for rectal administration. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed.

Sustained, pro-drugs, or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the ligands and use the lyophilizates obtained, for example, for the preparation of products for injection.

Aspects of the invention also include a coating for medical equipment. Alternatively, the peptides can be impregnated into a polymeric medical device such as catheters, stents and prosthetics. Coatings suitable for use in medical devices can be provided by a powder containing the peptides or by polymeric coating into which the peptides are suspended. Suitable polymeric materials for coatings or devices are those which are physiologically acceptable and through which a therapeutically effective amount of the peptide agent can diffuse. Suitable polymers include, but are not limited to, polyurethane, polymethacrylate, polyamide, polyester, polyethylene, polypropylene, polystyrene, polytetrafluoroethylene, polyvinyl-chloride, cellulose acetate, silicone elastomers, collagen, silk, etc. Such coatings are described, for instance, in U.S. Patent No. 4,612,337, issued September 16, 1986 to Fox et al. which is incorporated herein by reference.

It will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the specific compound being utilized, the particular compositions formulated, the mode of

application, and the particular situs and organism being treated. The materials and methods and the experiments presented above are detailed in Su et al., *J. Exp. Med.*, 189 (2):395-402 (1999). The example below discloses the materials and methods used to perform many of the experiments described above.

5

EXAMPLE 1

Reagents and cells.

Recombinant human (rh) SAA was purchased from Pepro Tech Inc. (Rocky Hill, NJ) with the sequence as follows:

10

MRSFFSFLGEAFDGMWRAYSMDREANYIGSDKYFHARGNYDAAKRGPGGVWAAEAI SNARENIQRFFGRGAEDS
LADQAANEWGRSGKDPNHFRPAGLPEKY. (SEQ. ID. No. 1). This rhSAA corresponds to SAA-1 α , one of the
major SAA isoforms in the serum, except for the addition of a methionine at the NH₂ terminus as well as the
substitution of aspartic acid for asparagine at position 60, which appears in the SAA2 isoform (reviewed in
ref. Steinkasserer et al., *Biochem. J.*, 268:187-193 (1990)). rhSAA at concentrations used in the study was
negative for endotoxin as assessed by Limulus amebocyte lysate assays (sensitivity: 0.06 IU/ml. BioWhittaker,
Walkersville, MD). High density lipoprotein (HDL) was purchased from Sigma (St. Louis, MO). Human peripheral
blood enriched in mononuclear cells or neutrophils was obtained from normal donors by leukapheresis (courtesy
of Transfusion Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD). The blood
was centrifuged through Ficoll-Hypaque (Sigma) and mononuclear cells (PBMC) collected at the interphase
were washed with PBS and centrifuged through a 46% isoosmotic Percoll (Pharmacia, Uppsala, Sweden)
gradient followed by elutriation to yield monocytes (purity: >90%). Neutrophils were purified by 3%
dextran/PBS sedimentation as described elsewhere (Badolato et al., *J. Exp. Med.*, 180:203-209 (1994)) and
were more than 98% pure. The cells were resuspended in RPMI 1640 medium containing 10% FCS (Hyclone,
Logan, UT) for future use. The molecular cloning of the receptors for fMLP was described previously (Murphy
et al., *J. Biol. Chem.*, 267:7637-7643 (1992); Gao, J.L. and P.M. Murphy, *J. Biol. Chem.*, 268:25395-25401
(1993); Murphy, P.M. and D. McDermott, *J. Biol. Chem.*, 266:12560-12567 (1991); and Ali et al., *J. Biol.
Chem.*, 273:11012-11016 (1998)). The cDNAs encoding classical formyl peptide receptor FPR and its variant
FPRL1 were stably transfected into human embryonic kidney epithelial cell line 293 that were cultured in
DMEM in the presence of 800 μ g/ml geneticin (G418, GibcoBRL, Grand Island, NY) to maintain selection. A rat
basophil leukemia cell line stably transfected with FPR (ETFR cells) was also used in the study (a kind gift
from Drs. H. Ali and R. Snyderman, Duke University Medical Center, NC).

30

Chemotaxis.

The migration of human 293 cells expressing FPR (FPR/293) or FPRL1 (FPRL1/293) as well as ETFR
cells was assessed by a 48-well microchemotaxis chamber technique (Falk et al., *J. Immunol. Methods*,
33:239-247 (1980); and Gong et al., *J. Biol. Chem.* 272:11682-11685 (1997)). A 25 μ l aliquot of rhSAA or
other reagents diluted in chemotaxis medium (RPMI1640, 1% BSA, 25 mM HEPES) was placed in the wells of

35

the lower compartment, and 50 μ l cell suspension (1×10^6 cell/ml in chemotaxis medium) were placed in the wells of the upper compartment of the chamber (Neuroprobe, Cabin John, MD). The two compartments were separated by a polycarbonate filter (10 μ m pore size, Neuroprobe) coated with 50 μ g/ml collagen type I (GIBCO, Gaithersburg, MD) for 1 h at 37°C. The chamber was incubated at 37°C for 5 h in humidified air with 5% CO₂. At the end of the incubation, the filter was removed, fixed and stained with Diff-Quik (Harlew, Gibbstown, NJ). The number of migrated cells in three high-powered fields (400 x) were counted by light microscopy after coding the samples. Results are expressed as the mean (\pm SD) value of the migration in triplicate samples and are representative of at least 5 experiments performed. For better illustration, chemotaxis indexes (CI) reflecting the fold increase of cell migration in response to stimulant over medium are used. Statistical significance of the difference between numbers of cells migrating in response to stimuli versus baseline (migration toward control medium) was calculated with Student's T test and the CI ≥ 2 are statistically significant.

Calcium mobilization.

Calcium mobilization was assayed by incubating 10^7 /ml of monocytes, neutrophils or receptor cDNA transfectants in loading buffer containing 138 mM NaCl, 6 mM KCl, 1 mM CaCl₂, 10 mM HEPES (pH 7.4), 5 mM Glucose, 0.1% BSA with 5 μ M Fura-2 (Sigma) at 37°C for 30 min. The dye-loaded cells were washed and resuspended in fresh loading buffer. The cells were then transferred into quartz cuvettes (10^6 cells in 2 ml) which were placed in a luminescence spectrometer LS50 B (Perkin-Elmer Limited, Beaconsfield, England). Stimulants at different concentrations were added in a volume of 20 μ l to the cuvettes at indicated time points. The ratio of fluorescence at 340 and 380 nm wavelength was calculated using the FL WinLab program. The assays were performed at least 5 times and results from representative experiments are shown.

Ligand binding assays.

rhSAA (20 μ g) was radio-iodinated on tyrosine and lysine residues with the chloramine T method and the specific activity of the labeled SAA was 5.8 mCi/mg (courtesy of J. Dobbs, SAIC Frederick, NCI-FCRDC, Frederick, MD). A constant concentration of 16 nM ¹²⁵I-SAA was incubated for 20 min at 37°C with human monocytes or 293 cells transfected with chemoattractant receptor cDNAs (1.5×10^6 /sample, in 200 μ l RPMI1640, 1% BSA, 0.05% NaN₃) in the presence of increasing concentrations of unlabeled SAA. After incubation, the cells were washed once with ice-cold PBS then were layered onto a 10% sucrose/PBS cushion in Eppendorf tubes. The cells were centrifuged at 10,000g for 1 min and the tips of the tubes containing cell pellets were cut and measured for radioactivity in a γ -counter. The binding data were analyzed and plotted with a computer-aided program LIGAND (P. Munson, Division of Computer Research and Technology, NIH, Bethesda, MD). The level of specific binding was determined by subtraction of non-specific binding (cpm on

cells in the presence of 1 μ M unlabeled SAA) from the total binding (cpm on cells in the absence of unlabeled SAA). Experiments were performed at least 5 times which yielded similar results.

Although the invention has been described with reference to embodiments and examples, it should be understood that various modifications can be made without departing from the spirit of the invention.

5 Accordingly, the invention is limited only by the following claims.

WHAT IS CLAIMED IS:

1. An isolated complex comprising a peptide agent having a sequence that corresponds to Serum amyloid A (SAA) or a conservative variant or functional fragment thereof bound to a molecule of FPRL1.
- 5 2. A polypeptide fragment of SAA that inhibits assembly of an SAA/FPRL1 complex by interacting with a FPRL1 receptor.
3. A nucleic acid encoding the polypeptide of Claim 2.
4. A polypeptide fragment of FPRL1 that inhibits assembly of an SAA/FPRL1 complex by interacting with a FPRL1 receptor.
- 10 5. A nucleic acid encoding the polypeptide of Claim 4.
6. A method of inhibiting assembly of an SAA/FPRL1 complex comprising the steps of:
administering the polypeptide of Claims 2 or 4; and
measuring the effect of the polypeptide as a ligand that interacts with a FPRL1 receptor.
7. A method of identifying an agent that modulates the assembly of an SAA/FPRL1 complex
15 comprising:
providing a support having disposed thereon a molecule of SAA;
contacting the support with a candidate agent in the presence of a molecule of FPRL1;
detecting the presence or absence of an SAA/FPRL1 complex; and
identifying the agent as a molecule that promotes assembly of the SAA/FPRL1 complex or
20 inhibits assembly of the SAA/FPRL1 complex.
8. A polypeptide fragment of SAA or FPRL1 identified by the method of Claim 7.
9. A peptidomimetic that resembles the polypeptide fragment of Claim 8.
10. A nucleic acid encoding at least a portion of SAA or FPRL1 identified by the method of Claim 7.
- 25 11. A method of modulating a cellular response in a subject comprising:
identifying a subject in need of a peptide agent that modulates a SAA/FPRL1 complex; and
administering to the subject an amount of the peptide agent sufficient to modulate a cellular response, wherein the peptide agent comprises a sequence that corresponds to Serum amyloid A (SAA) or FPRL1, or conservative variants or functional fragments thereof.
- 30 12. The method of Claim 11, wherein the peptide agent is SAA having at least one acidic amino acid replaced with a different acidic amino acid.
13. The method of Claim 11, wherein the peptide agent is Serum amyloid A (SAA) having at least one basic amino acid replaced with a different basic amino acid.
14. The method of Claim 11, wherein the peptide agent is Serum amyloid A (SAA) having at
35 least one nonpolar amino acid replaced with a different nonpolar amino acid.

15. The method of Claim 11, wherein the peptide agent is Serum amyloid A (SAA) having at least one uncharged amino acid replaced with a different uncharged amino acid.

16. The method of Claim 11, wherein the peptide agent is Serum amyloid A (SAA) having at least one aromatic amino acid replaced with a different aromatic amino acid.

5 17. A method of modulating a cellular response in a subject comprising:
administering to the subject an amount of a peptide agent having a sequence that corresponds to Serum amyloid A (SAA) or FPRL1 or conservative variants or functional fragments thereof sufficient to modulate a cellular response; and
measuring the effect of the peptide agent as a ligand that interacts with a FPRL1 receptor.

10 18. The method of Claim 17, wherein the peptide agent is Serum amyloid A (SAA) or FPRL1 having at least one acidic amino acid replaced with a different acidic amino acid.

19. The method of Claim 17, wherein the peptide agent is Serum amyloid A (SAA) or FPRL1 having at least one basic amino acid replaced with a different basic amino acid.

15 20. The method of Claim 17, wherein the peptide agent is Serum amyloid A (SAA) or FPRL1 having at least one nonpolar amino acid replaced with a different nonpolar amino acid.

21. The method of Claim 17, wherein the peptide agent is Serum amyloid A (SAA) or FPRL1 having at least one uncharged amino acid replaced with a different uncharged amino acid.

22. The method of Claim 17, wherein the peptide agent is Serum amyloid A (SAA) or FPRL1 having at least one aromatic amino acid replaced with a different aromatic amino acid.

20 23. A method of making a pharmaceutical product comprising:
providing a peptide agent having a sequence corresponding to Serum amyloid A (SAA) or FPRL1, or conservative variants or functional fragments thereof;
providing a cell having a molecule of FPRL1 that interacts with the peptide agent;
contacting the peptide agent with the cell under conditions that allow the peptide agent to
25 interact with the FPRL1 molecule on the cell;
identifying the presence or absence of signal transduction generated in response to the interaction of the peptide agent with the FPRL1 molecule; and
incorporating the peptide into the pharmaceutical product.

30 24. The method of Claim 23, wherein the peptide agent is Serum amyloid A (SAA) having at least one acidic amino acid replaced with a different acidic amino acid.

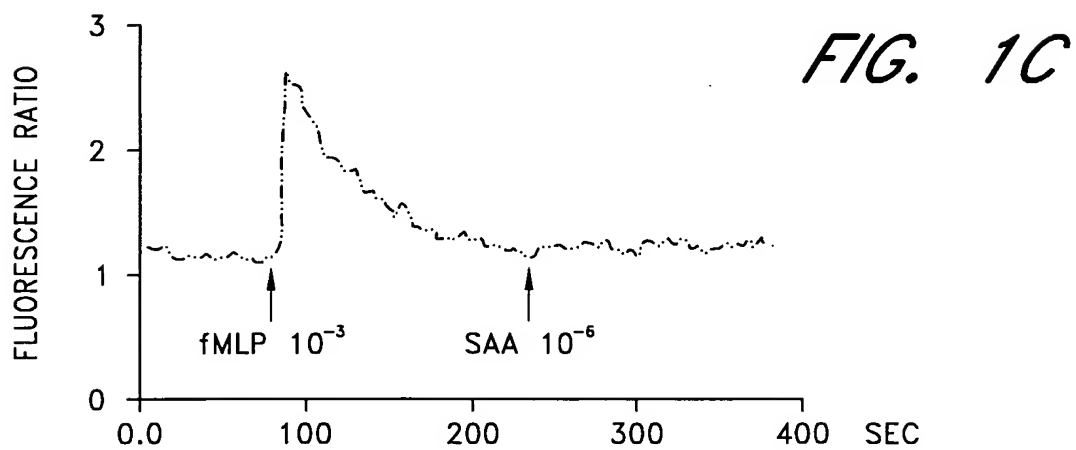
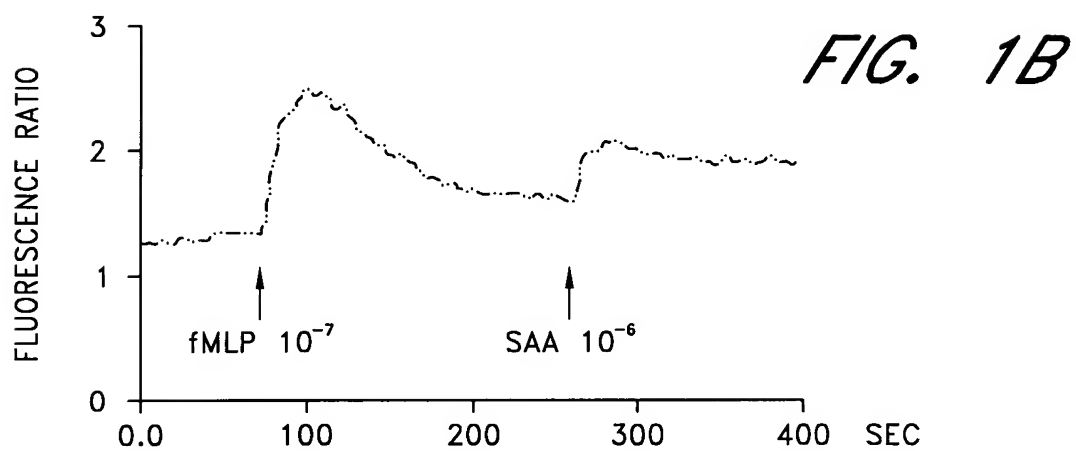
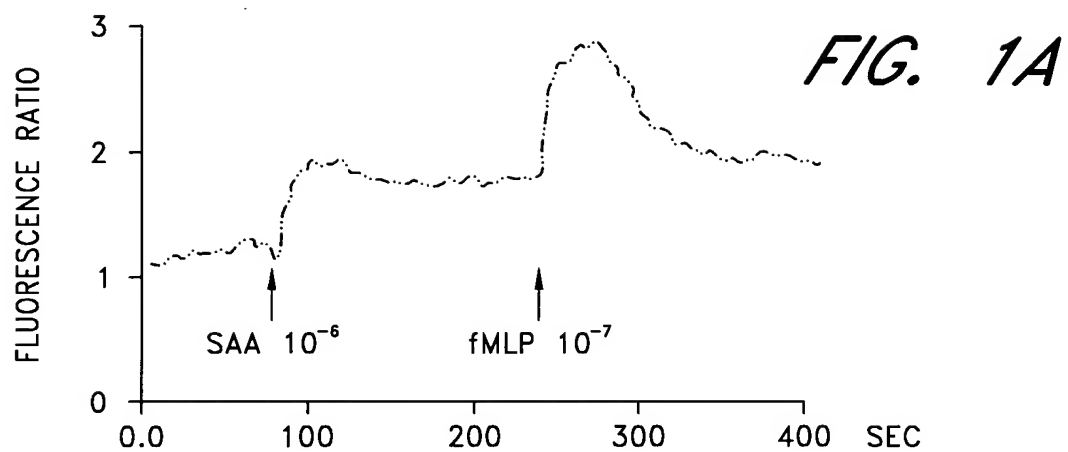
25. The method of Claim 23, wherein the peptide agent is Serum amyloid A (SAA) having at least one basic amino acid replaced with a different basic amino acid.

26. The method of Claim 23, wherein the peptide agent is Serum amyloid A (SAA) having at least one nonpolar amino acid replaced with a different nonpolar amino acid.

35 27. The method of Claim 23, wherein the peptide agent is Serum amyloid A (SAA) having at least one uncharged amino acid replaced with a different uncharged amino acid.

28. The method of Claim 23, wherein the peptide agent is Serum amyloid A (SAA) having at least one aromatic amino acid replaced with a different aromatic amino acid.

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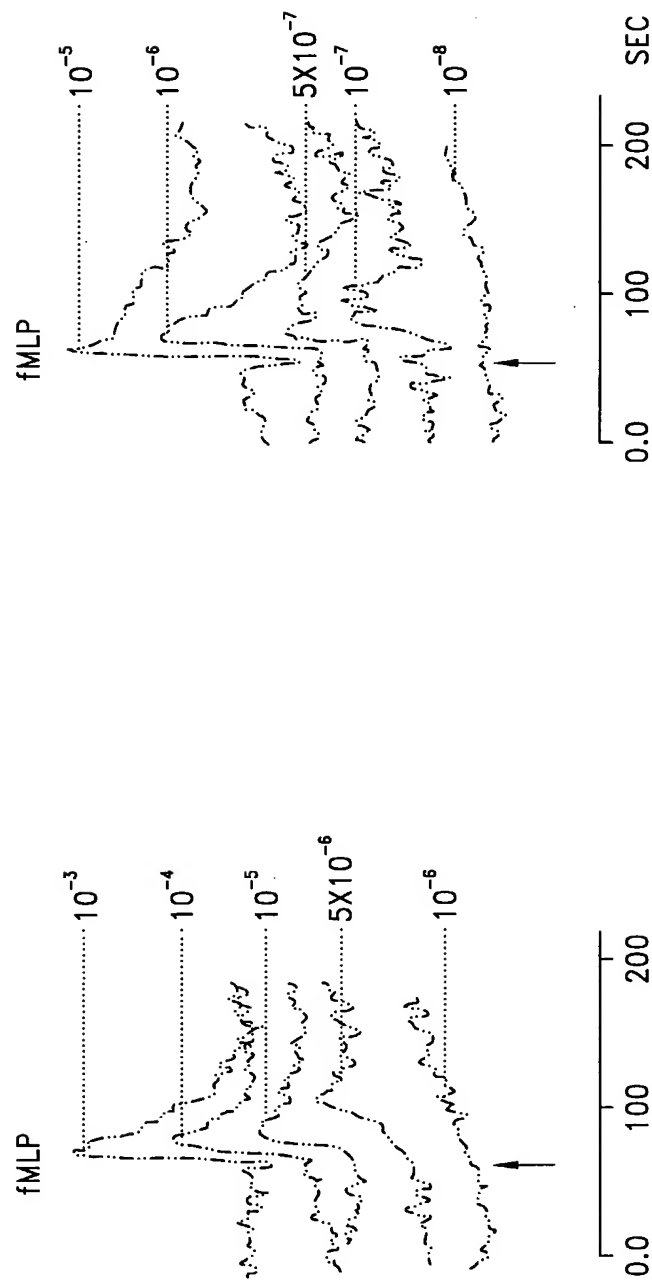


FIG. 2A

FIG. 2B

FIG. 2D

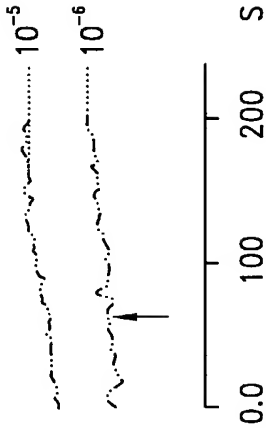
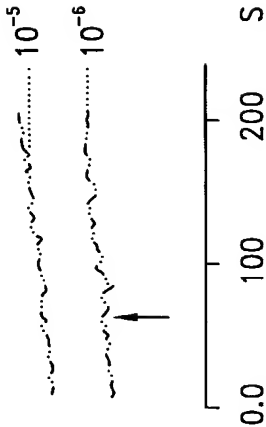
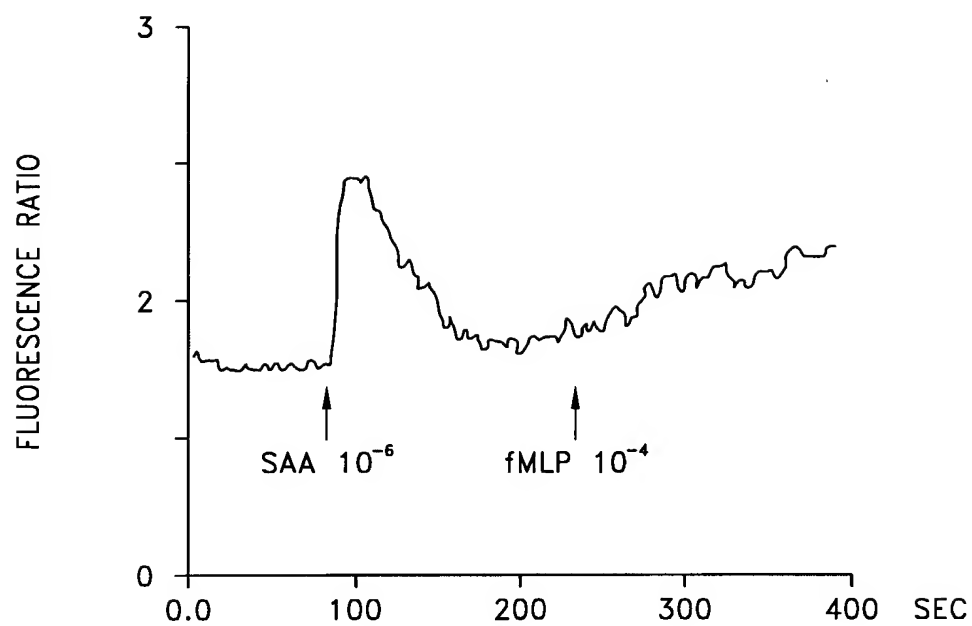
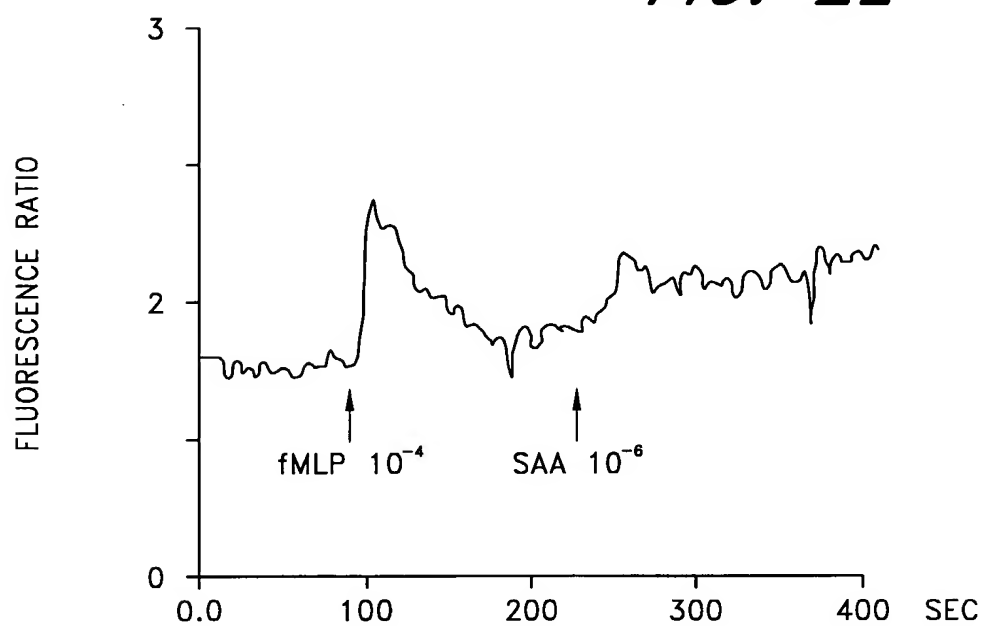


FIG. 2C



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*FIG. 2E**FIG. 2F*

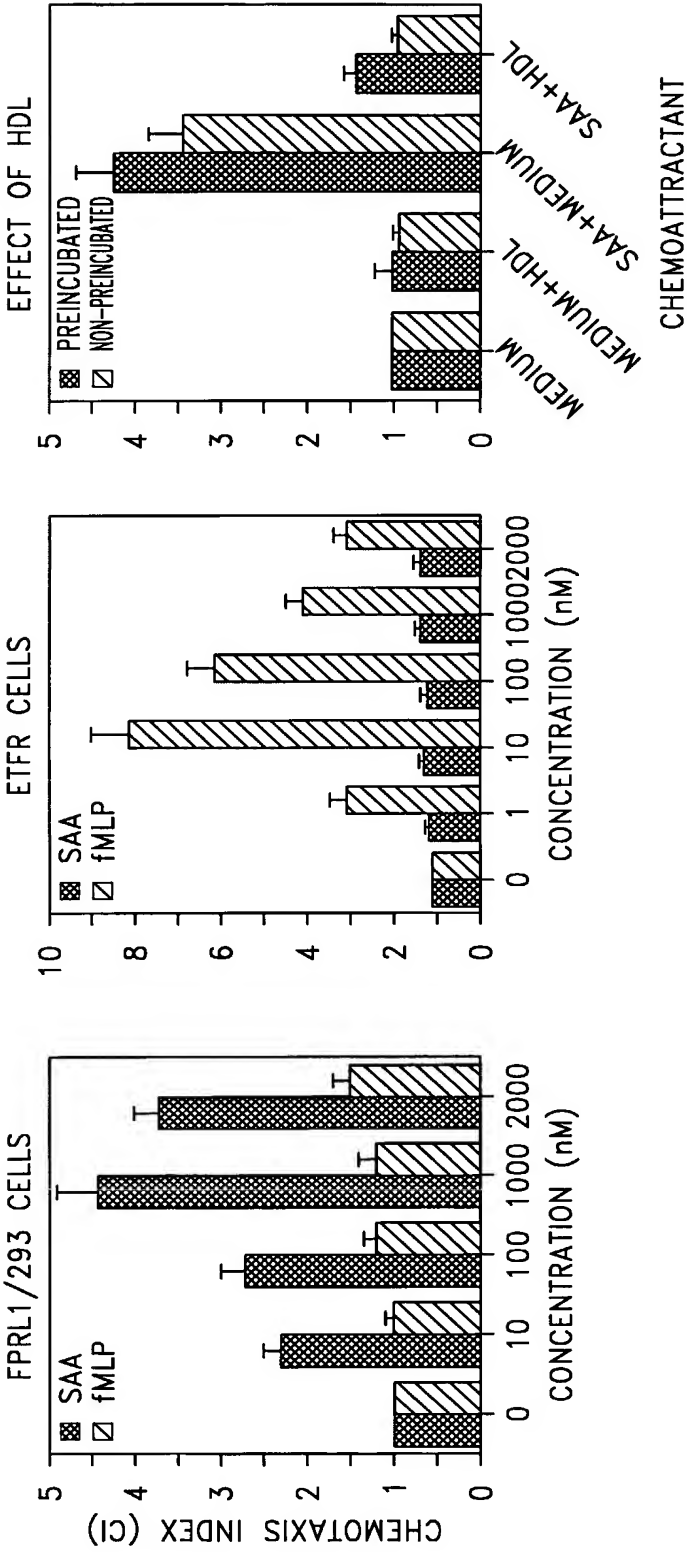


FIG. 3A

FIG. 3B

FIG. 3C

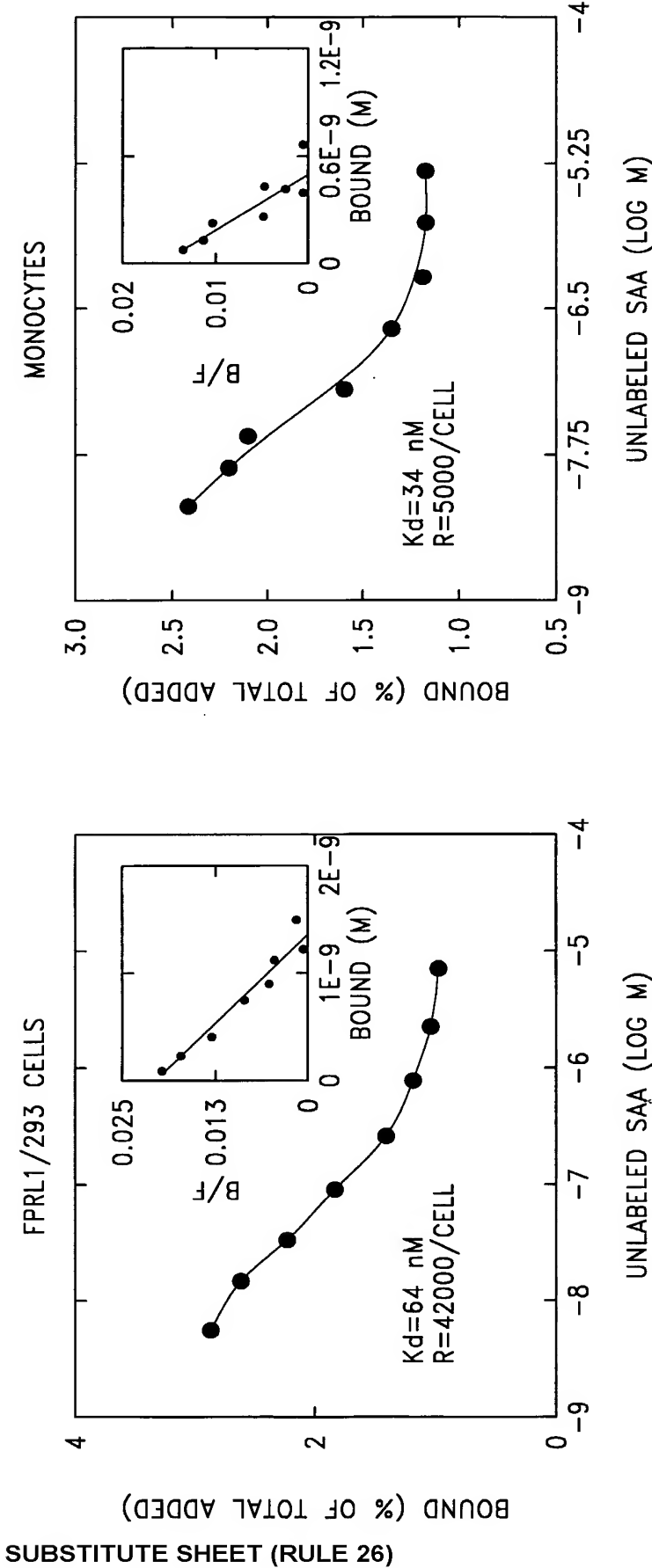


FIG. 4B

FIG. 4A

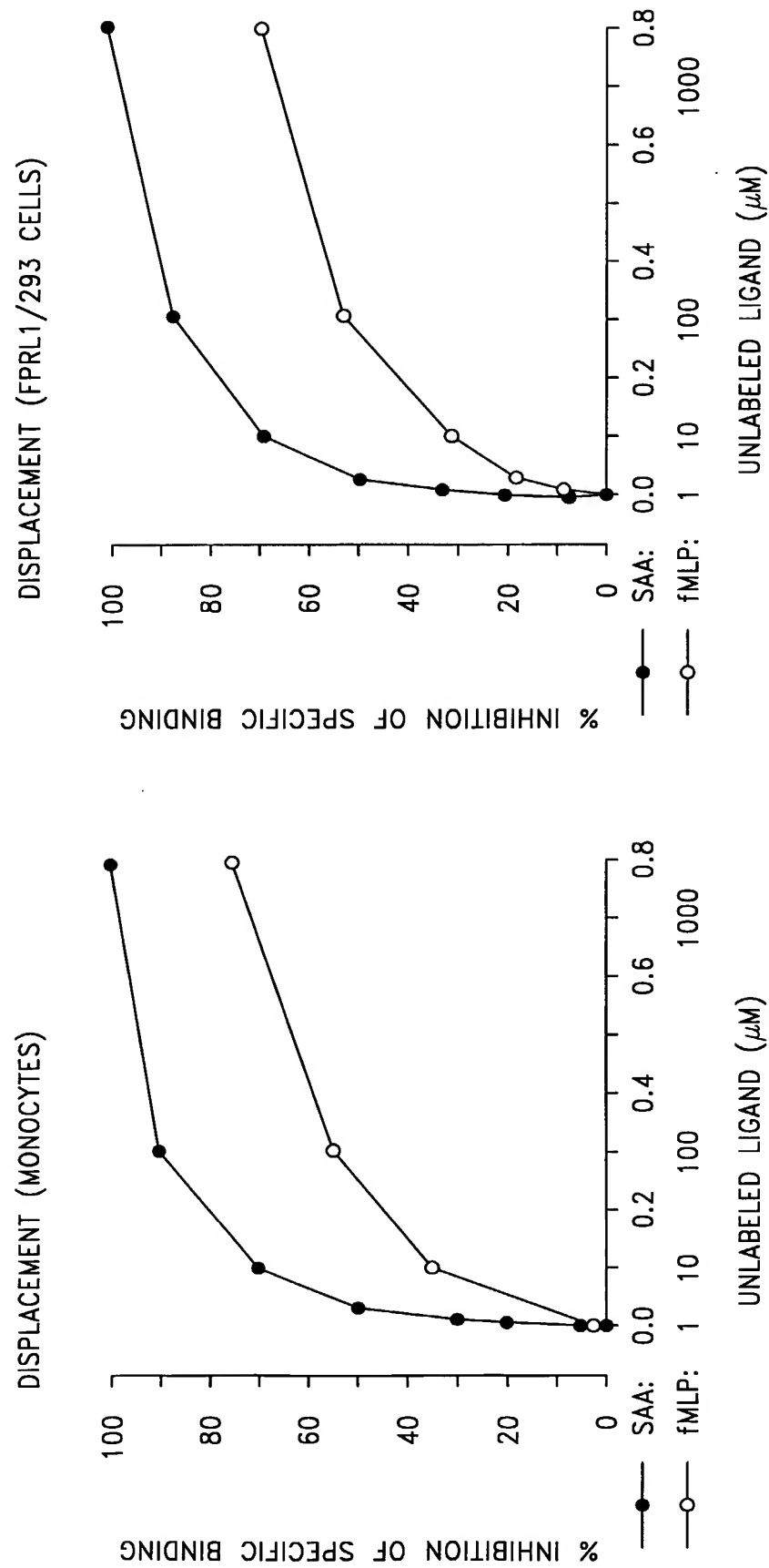


FIG. 4C

FIG. 4D

SEQUENCE LISTING

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 Joost J. Oppenheim
 Shao-Bo Su
 Wang-Hua Gong
 Ji-Liang Gao
 Philip M. Murphy

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 <213> Homo Sapiens

<400> 27
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn
 20 25

<210> 28
 <211> 30
 <212> PRT
 <213> Homo Sapiens

<400> 28
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr
 20 25 30

<210> 29
 <211> 31
 <212> PRT
 <213> Homo Sapiens

<400> 29
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
 20 25 30

<210> 30
 <211> 32
 <212> PRT
 <213> Homo Sapiens

<400> 30
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30

<210> 31
 <211> 33
 <212> PRT
 <213> Homo Sapiens

<400> 31
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser

<210> 32
 <211> 34
 <212> PRT
 <213> Homo Sapiens

<400> 32
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp

<210> 33
 <211> 35
 <212> PRT
 <213> Homo Sapiens

<400> 33
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys
 35

<210> 34

<211> 36
 <212> PRT
 <213> Homo Sapiens

<400> 34
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr
 35

<210> 35
 <211> 37
 <212> PRT
 <213> Homo Sapiens

<400> 35
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe
 35

<210> 36
 <211> 38
 <212> PRT
 <213> Homo Sapiens

<400> 36
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His
 35

<210> 37
 <211> 39
 <212> PRT
 <213> Homo Sapiens

<400> 37
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala
 35

<210> 38
 <211> 40
 <212> PRT
 <213> Homo Sapiens

<400> 38
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg

35

40

<210> 39

<211> 41

<212> PRT

<213> Homo Sapiens

<400> 39

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
			20					25					30		
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly							
		35					40								

<210> 40

<211> 42

<212> PRT

<213> Homo Sapiens

<400> 40

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
			20					25					30		
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn						
		35					40								

<210> 41

<211> 43

<212> PRT

<213> Homo Sapiens

<400> 41

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
			20					25					30		
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr					
		35					40								

<210> 42

<211> 44

<212> PRT

<213> Homo Sapiens

<400> 42

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
			20					25					30		
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp				
		35					40								

<210> 43

<211> 45

<212> PRT

<213> Homo Sapiens

<400> 43

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	

Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala
 35 40 45

<210> 44
 <211> 46
 <212> PRT
 <213> Homo Sapiens

<400> 44
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala
 35 40 45

<210> 45
 <211> 47
 <212> PRT
 <213> Homo Sapiens

<400> 45
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
 35 40 45

<210> 46
 <211> 48
 <212> PRT
 <213> Homo Sapiens

<400> 46
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45

<210> 47
 <211> 49
 <212> PRT
 <213> Homo Sapiens

<400> 47
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45

Gly

<210> 48
 <211> 50
 <212> PRT

<213> Homo Sapiens

<400> 48

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro
 50

<210> 49

<211> 51

<212> PRT

<213> Homo Sapiens

<400> 49

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly
 50

<210> 50

<211> 52

<212> PRT

<213> Homo Sapiens

<400> 50

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly
 50

<210> 51

<211> 53

<212> PRT

<213> Homo Sapiens

<400> 51

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val
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<210> 52

<211> 54

<212> PRT

<213> Homo Sapiens

<400> 52

Met	Arg	Ser	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1			5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile
			20					25					30	Gly
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys
			35					40					45	Arg
Gly	Pro	Gly	Gly	Val	Trp									
	50													

<210> 53

<211> 55

<212> PRT

<213> Homo Sapiens

<400> 53

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala
1			5						10					15
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile
			20					25					30	Gly
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys
			35					40					45	Arg
Gly	Pro	Gly	Gly	Val	Trp	Ala								
	50					55								

<210> 54

<211> 56

<212> PRT

<213> Homo Sapiens

<400> 54

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala
1			5						10					15
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile
			20					25					30	Gly
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys
			35					40					45	Arg
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala							
	50					55								

<210> 55

<211> 57

<212> PRT

<213> Homo Sapiens

<400> 55

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala
1			5						10					15
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile
			20					25					30	Gly
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys
			35					40					45	Arg
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu						
	50					55								

<210> 56

<211> 58

<212> PRT

<213> Homo Sapiens

<400> 56

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala
														Arg

1		5		10		15									
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
		20		25		30									
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg
		35		40		45									
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala						
	50					55									

<210> 57

<211> 59

<212> PRT

<213> Homo Sapiens

<400> 57

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1			5					10					15		
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
		20		25		30									
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg
		35		40		45									
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile					
	50					55									

<210> 58

<211> 60

<212> PRT

<213> Homo Sapiens

<400> 58

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1			5					10					15		
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
		20		25		30									
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg
		35		40		45									
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser				
	50					55					60				

<210> 59

<211> 61

<212> PRT

<213> Homo Sapiens

<400> 59

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1			5					10					15		
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
		20		25		30									
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg
		35		40		45									
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn			
	50					55					60				

<210> 60

<211> 62

<212> PRT

<213> Homo Sapiens

<400> 60

Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1			5					10					15		
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly

20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala
 50 55 60

<210> 61
 <211> 63
 <212> PRT
 <213> Homo Sapiens

<400> 61
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg
 50 55 60

<210> 62
 <211> 64
 <212> PRT
 <213> Homo Sapiens

<400> 62
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60

<210> 63
 <211> 66
 <212> PRT
 <213> Homo Sapiens

<400> 63
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile
 65

<210> 64
 <211> 67
 <212> PRT
 <213> Homo Sapiens

<400> 64
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly

20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln
 65

<210> 65
 <211> 68
 <212> PRT
 <213> Homo Sapiens

<400> 65
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg
 65

<210> 66
 <211> 69
 <212> PRT
 <213> Homo Sapiens

<400> 66
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe
 65

<210> 67
 <211> 70
 <212> PRT
 <213> Homo Sapiens

<400> 67
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe
 65 70

<210> 68
 <211> 71
 <212> PRT

<213> Homo Sapiens

<400> 68

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60
Asn Ile Gln Arg Phe Phe Gly
65           70

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<210> 69

<211> 72

<212> PRT

<213> Homo Sapiens

<400> 69

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60
Asn Ile Gln Arg Phe Phe Gly Arg
65           70

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<210> 70

<211> 73

<212> PRT

<213> Homo Sapiens

<400> 70

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60
Asn Ile Gln Arg Phe Phe Gly Arg Gly
65           70

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<210> 71

<211> 74

<212> PRT

<213> Homo Sapiens

<400> 71

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60

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Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala
65 70

<210> 72
<211> 75
<212> PRT
<213> Homo Sapiens

<400> 72
Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
1 5 10 15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
20 25 30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
35 40 45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
50 55 60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu
65 70 75

<210> 73
<211> 76
<212> PRT
<213> Homo Sapiens

<400> 73
Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
1 5 10 15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
20 25 30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
35 40 45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
50 55 60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp
65 70 75

<210> 74
<211> 77
<212> PRT
<213> Homo Sapiens

<400> 74
Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
1 5 10 15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
20 25 30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
35 40 45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
50 55 60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser
65 70 75

<210> 75
<211> 78
<212> PRT
<213> Homo Sapiens

<400> 75
Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
1 5 10 15

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<210> 76
<211> 79
<212> PRT
<213> Homo Sapiens
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<210> 77
<211> 80
<212> PRT
<213> Homo Sapiens
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<210> 78
<211> 81
<212> PRT
<213> Homo Sapiens
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17

<210> 79
 <211> 82
 <212> PRT
 <213> Homo Sapiens

<400> 79
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala

<210> 80
 <211> 83
 <212> PRT
 <213> Homo Sapiens

<400> 80
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala

<210> 81
 <211> 84
 <212> PRT
 <213> Homo Sapiens

<400> 81
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn

<210> 82
 <211> 85
 <212> PRT
 <213> Homo Sapiens

<400> 82
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu
 85

<210> 83
 <211> 86
 <212> PRT
 <213> Homo Sapiens

<400> 83
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp
 85

<210> 84
 <211> 87
 <212> PRT
 <213> Homo Sapiens

<400> 84
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly
 85

<210> 85
 <211> 88
 <212> PRT
 <213> Homo Sapiens

<400> 85
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30

Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg
 85

<210> 86

<211> 89

<212> PRT

<213> Homo Sapiens

<400> 86

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser
 85

<210> 87

<211> 90

<212> PRT

<213> Homo Sapiens

<400> 87

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly
 85 90

<210> 88

<211> 91

<212> PRT

<213> Homo Sapiens

<400> 88

Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp

65 70 75
Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys
 85 90

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<210> 89
<211> 92
<212> PRT
<213> Homo Sapiens
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<400> 89															
Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
			20					25					30		
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg
		35					40					45			
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu
		50				55					60				
Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp
65					70					75					80
Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp				
				85					90						

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<210> 90
<211> 93
<212> PRT
<213> Homo Sapiens
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<div> <div><400></div> <div>90</div> </div>															
Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg
1				5					10					15	
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly
			20					25					30		
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg
		35					40					45			
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu
		50				55					60				
Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp
65					70					75					80
Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro			
				85					90						

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<210> 91
<211> 94
<212> PRT
<213> Homo Sapiens
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			<400>	91												
Met	Arg	Ser	Phe	Phe	Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg	
1				5					10					15		
Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly	
			20					25					30			
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg	
		35					40					45				
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	
		50				55					60					
Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	
65					70					75					80	
Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn			
				85					90							

<210> 92

<211> 95
 <212> PRT
 <213> Homo Sapiens

<400> 92
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 85 90 95

<210> 93
 <211> 96
 <212> PRT
 <213> Homo Sapiens

<400> 93
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 85 90 95

<210> 94
 <211> 97
 <212> PRT
 <213> Homo Sapiens

<400> 94
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 85 90 95
 Arg

<210> 95
 <211> 98
 <212> PRT
 <213> Homo Sapiens

<400> 95
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 85 90 95
 Arg Pro

<210> 96
 <211> 99
 <212> PRT
 <213> Homo Sapiens

<400> 96
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 85 90 95
 Arg Pro Ala

<210> 97
 <211> 100
 <212> PRT
 <213> Homo Sapiens

<400> 97
 Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1 5 10 15
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 20 25 30
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 35 40 45
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50 55 60
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 65 70 75 80
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 85 90 95
 Arg Pro Ala Gly
 100

<210> 98
 <211> 101
 <212> PRT

<213> Homo Sapiens

<400> 98

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
65           70           75           80
Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
          85           90           95
Arg Pro Ala Gly Leu
          100

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<210> 99

<211> 102

<212> PRT

<213> Homo Sapiens

<400> 99

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
65           70           75           80
Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
          85           90           95
Arg Pro Ala Gly Leu Pro
          100

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<210> 100

<211> 103

<212> PRT

<213> Homo Sapiens

<400> 100

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
          50           55           60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
65           70           75           80
Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
          85           90           95
Arg Pro Ala Gly Leu Pro Glu
          100

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<210> 101

<211> 104

<212> PRT

<213> Homo Sapiens

<400> 101

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Met Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg
 1           5           10           15
Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
          20           25           30
Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
          35           40           45
Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 50           55           60
Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
65           70           75           80
Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
          85           90           95
Arg Pro Ala Gly Leu Pro Glu Lys
          100

```

<210> 102

<211> 104

<212> PRT

<213> Homo Sapiens

<400> 102

```

Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp
 1           5           10           15
Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser
          20           25           30
Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly
          35           40           45
Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn
 50           55           60
Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
65           70           75           80
Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
          85           90           95
Pro Ala Gly Leu Pro Glu Lys Tyr
          100

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<210> 103

<211> 103

<212> PRT

<213> Homo Sapiens

<400> 103

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Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met
 1           5           10           15
Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp
          20           25           30
Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro
          35           40           45
Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile
 50           55           60
Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
65           70           75           80
Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
          85           90           95
Ala Gly Leu Pro Glu Lys Tyr
          100

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<210> 104

<211> 102
 <212> PRT
 <213> Homo Sapiens

<400> 104
 Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp
 1 5 10 15
 Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys
 20 25 30
 Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly
 35 40 45
 Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
 50 55 60
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 65 70 75 80
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 85 90 95
 Gly Leu Pro Glu Lys Tyr
 100

<210> 105
 <211> 101
 <212> PRT
 <213> Homo Sapiens

<400> 105
 Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg
 1 5 10 15
 Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr
 20 25 30
 Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly
 35 40 45
 Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg
 50 55 60
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
 65 70 75 80
 Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
 85 90 95
 Leu Pro Glu Lys Tyr
 100

<210> 106
 <211> 100
 <212> PRT
 <213> Homo Sapiens

<400> 106
 Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala
 1 5 10 15
 Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe
 20 25 30
 His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val
 35 40 45
 Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
 50 55 60
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 65 70 75 80
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 85 90 95
 Pro Glu Lys Tyr
 100

<210> 107
 <211> 99
 <212> PRT
 <213> Homo Sapiens

<400> 107
 Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr
 1 5 10 15
 Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His
 20 25 30
 Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Val Trp
 35 40 45
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 50 55 60
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 65 70 75 80
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 85 90 95
 Glu Lys Tyr

<210> 108
 <211> 98
 <212> PRT
 <213> Homo Sapiens

<400> 108
 Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser
 1 5 10 15
 Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala
 20 25 30
 Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala
 35 40 45
 Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly
 50 55 60
 Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
 65 70 75 80
 Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
 85 90 95
 Lys Tyr

<210> 109
 <211> 97
 <212> PRT
 <213> Homo Sapiens

<400> 109
 Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp
 1 5 10 15
 Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg
 20 25 30
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 35 40 45
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 50 55 60
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 65 70 75 80
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 85 90 95
 Tyr

<210> 110
 <211> 96
 <212> PRT
 <213> Homo Sapiens

<400> 110
 Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met
 1 5 10 15
 Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly
 20 25 30
 Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu
 35 40 45
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 50 55 60
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 65 70 75 80
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85 90 95

<210> 111
 <211> 95
 <212> PRT
 <213> Homo Sapiens

<400> 111
 Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg
 1 5 10 15
 Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn
 20 25 30
 Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala
 35 40 45
 Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala
 50 55 60
 Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly
 65 70 75 80
 Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85 90 95

<210> 112
 <211> 94
 <212> PRT
 <213> Homo Sapiens

<400> 112
 Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu
 1 5 10 15
 Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr
 20 25 30
 Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile
 35 40 45
 Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu
 50 55 60
 Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys
 65 70 75 80
 Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85 90

<210> 113
 <211> 93
 <212> PRT
 <213> Homo Sapiens

<400> 113

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Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala
 1           5           10           15
Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp
          20           25           30
Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser
          35           40           45
Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp
          50           55           60
Ser Leu Ala Asp Gln Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp
65           70           75           80
Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
          85           90

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<210> 114

<211> 92

<212> PRT

<213> Homo Sapiens

<400> 114

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Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn
 1           5           10           15
Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala
          20           25           30
Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn
          35           40           45
Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser
          50           55           60
Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro
65           70           75           80
Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
          85           90

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<210> 115

<211> 91

<212> PRT

<213> Homo Sapiens

<400> 115

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Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr
 1           5           10           15
Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala
          20           25           30
Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala
          35           40           45
Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu
          50           55           60
Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn
65           70           75           80
His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
          85           90

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<210> 116

<211> 90

<212> PRT

<213> Homo Sapiens

<400> 116

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Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
 1           5           10           15
Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys

```

		20						25				30					
Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg		
		35					40					45					
Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala		
	50					55				60							
Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His		
65				70						75					80		
Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr								
				85					90								

<210> 117

<211> 89

<212> PRT

<213> Homo Sapiens

<400> 117

Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly		
1				5					10					15			
Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg		
			20					25					30				
Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu		
		35				40						45					
Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp		
	50					55				60							
Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe		
65				70						75					80		
Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr									
				85													

<210> 118

<211> 88

<212> PRT

<213> Homo Sapiens

<400> 118

Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly	Ser		
1				5					10					15			
Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg	Gly		
			20					25					30				
Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	Asn		
		35				40						45					
Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln		
	50					55				60							
Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg		
65				70						75					80		
Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr										
				85													

<210> 119

<211> 87

<212> PRT

<213> Homo Sapiens

<400> 119

Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly	Ser	Asp		
1				5					10					15			
Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg	Gly	Pro		
			20					25					30				
Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	Asn	Ile		
		35				40						45					
Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala		
	50					55					60						

Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 65 70 75 80
 Ala Gly Leu Pro Glu Lys Tyr
 85

<210> 120
 <211> 86
 <212> PRT
 <213> Homo Sapiens

<400> 120
 Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys
 1 5 10 15
 Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly
 20 25 30
 Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
 35 40 45
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 50 55 60
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 65 70 75 80
 Gly Leu Pro Glu Lys Tyr
 85

<210> 121
 <211> 84
 <212> PRT
 <213> Homo Sapiens

<400> 121
 Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe
 1 5 10 15
 His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val
 20 25 30
 Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
 35 40 45
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 50 55 60
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 65 70 75 80
 Pro Glu Lys Tyr

<210> 122
 <211> 83
 <212> PRT
 <213> Homo Sapiens

<400> 122
 Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His
 1 5 10 15
 Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp
 20 25 30
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 35 40 45
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 50 55 60
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 65 70 75 80
 Glu Lys Tyr

<210> 123
 <211> 82
 <212> PRT
 <213> Homo Sapiens

<400> 123
 Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala
 1 5 10 15
 Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala
 20 25 30
 Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly
 35 40 45
 Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
 50 55 60
 Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
 65 70 75 80
 Lys Tyr

<210> 124
 <211> 81
 <212> PRT
 <213> Homo Sapiens

<400> 124
 Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg
 1 5 10 15
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 20 25 30
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 35 40 45
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 50 55 60
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 65 70 75 80
 Tyr

<210> 125
 <211> 80
 <212> PRT
 <213> Homo Sapiens

<400> 125
 Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly
 1 5 10 15
 Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu
 20 25 30
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 35 40 45
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 50 55 60
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70 75 80

<210> 126
 <211> 79
 <212> PRT
 <213> Homo Sapiens

<400> 126
 Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn

1	5	10	15
Tyr Asp Ala	Ala Lys Arg Gly Pro Gly	Gly Val Trp Ala	Ala Glu Ala
	20	25	30
Ile Ser Asn	Ala Arg Glu Asn Ile Gln Arg Phe Phe	Gly Arg Gly Ala	
	35	40	45
Glu Asp Ser	Leu Ala Asp Gln Ala Ala Asn Glu Trp	Gly Arg Ser Gly	
	50	55	60
Lys Asp Pro	Asn His Phe Arg Pro Ala Gly Leu	Pro Glu Lys Tyr	
65	70	75	

<210> 127

<211> 78

<212> PRT

<213> Homo Sapiens

<400> 127

Ala Asn Tyr	Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly	Asn Tyr
1	5	10
15		
Asp Ala Ala	Lys Arg Gly Pro Gly Gly Val Trp Ala Ala	Glu Ala Ile
	20	25
30		
Ser Asn Ala	Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly	Ala Glu
	35	40
45		
Asp Ser Leu	Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly	Lys
	50	55
60		
Asp Pro Asn	His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr	
65	70	75

<210> 128

<211> 77

<212> PRT

<213> Homo Sapiens

<400> 128

Asn Tyr Ile	Gly Ser Asp Lys Tyr Phe His Ala Arg Gly	Asn Tyr Asp
1	5	10
15		
Ala Ala Lys	Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala	Ile Ser
	20	25
30		
Asn Ala Arg	Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly	Ala Glu Asp
	35	40
45		
Ser Leu Ala	Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly	Lys Asp
	50	55
60		
Pro Asn His	Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr	
65	70	75

<210> 129

<211> 76

<212> PRT

<213> Homo Sapiens

<400> 129

Tyr Ile Gly	Ser Asp Lys Tyr Phe His Ala Arg Gly	Asn Tyr Asp Ala
1	5	10
15		
Ala Lys Arg	Gly Pro Gly Gly Val Trp Ala Ala Glu Ala	Ile Ser Asn
	20	25
30		
Ala Arg Glu	Asn Ile Gln Arg Phe Gly Arg Gly Ala Glu	Asp Ser
	35	40
45		
Leu Ala Asp	Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly	Lys Asp Pro
	50	55
60		
Asn His Phe	Arg Pro Ala Gly Leu Pro Glu Lys Tyr	
65	70	75

<210> 130

<211> 75
 <212> PRT
 <213> Homo Sapiens

<400> 130
 Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala
 1 5 10 15
 Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala
 20 25 30
 Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu
 35 40 45
 Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn
 50 55 60
 His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70 75

<210> 131
 <211> 74
 <212> PRT
 <213> Homo Sapiens

<400> 131
 Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
 1 5 10 15
 Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg
 20 25 30
 Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala
 35 40 45
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 50 55 60
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 132
 <211> 73
 <212> PRT
 <213> Homo Sapiens

<400> 132
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 1 5 10 15
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 20 25 30
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 35 40 45
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 50 55 60
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 133
 <211> 72
 <212> PRT
 <213> Homo Sapiens

<400> 133
 Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly
 1 5 10 15
 Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn
 20 25 30
 Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
 35 40 45

Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 50 55 60
 Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 134
 <211> 71
 <212> PRT
 <213> Homo Sapiens

<400> 134
 Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro
 1 5 10 15
 Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile
 20 25 30
 Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
 35 40 45
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 50 55 60
 Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 135
 <211> 70
 <212> PRT
 <213> Homo Sapiens

<400> 135
 Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly
 1 5 10 15
 Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
 20 25 30
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 35 40 45
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 50 55 60
 Gly Leu Pro Glu Lys Tyr
 65 70

<210> 136
 <211> 69
 <212> PRT
 <213> Homo Sapiens

<400> 136
 Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly
 1 5 10 15
 Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg
 20 25 30
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
 35 40 45
 Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
 50 55 60
 Leu Pro Glu Lys Tyr
 65

<210> 137
 <211> 68
 <212> PRT
 <213> Homo Sapiens

<400> 137

His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val
 1 5 10 15
 Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
 20 25 30
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 35 40 45
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 50 55 60
 Pro Glu Lys Tyr
 65

<210> 138
 <211> 67
 <212> PRT
 <213> Homo Sapiens

<400> 138
 Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp
 1 5 10 15
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 20 25 30
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 35 40 45
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 50 55 60
 Glu Lys Tyr
 65

<210> 139
 <211> 66
 <212> PRT
 <213> Homo Sapiens

<400> 139
 Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala
 1 5 10 15
 Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly
 20 25 30
 Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
 35 40 45
 Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
 50 55 60
 Lys Tyr
 65

<210> 140
 <211> 65
 <212> PRT
 <213> Homo Sapiens

<400> 140
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 1 5 10 15
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 20 25 30
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 35 40 45
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 50 55 60
 Tyr
 65

<210> 141
 <211> 64
 <212> PRT
 <213> Homo Sapiens

<400> 141
 Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu
 1 5 10 15
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 20 25 30
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 35 40 45
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 142
 <211> 63
 <212> PRT
 <213> Homo Sapiens

<400> 142
 Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala
 1 5 10 15
 Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala
 20 25 30
 Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly
 35 40 45
 Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 143
 <211> 62
 <212> PRT
 <213> Homo Sapiens

<400> 143
 Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile
 1 5 10 15
 Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu
 20 25 30
 Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys
 35 40 45
 Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 144
 <211> 61
 <212> PRT
 <213> Homo Sapiens

<400> 144
 Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser
 1 5 10 15
 Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp
 20 25 30
 Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp
 35 40 45
 Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 145
 <211> 60

<212> PRT

<213> Homo Sapiens

<400> 145

Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn
1				5					10					15	
Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser
			20					25					30		
Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro
		35					40					45			
Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr				
50						55					60				

<210> 146

<211> 59

<212> PRT

<213> Homo Sapiens

<400> 146

Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala
1				5				10						15	
Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu
			20					25					30		
Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn
		35					40					45			
His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr					
50						55									

<210> 147

<211> 58

<212> PRT

<213> Homo Sapiens

<400> 147

Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg
1				5					10					15	
Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala
			20					25					30		
Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His
		35					40					45			
Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr						
50						55									

<210> 148

<211> 57

<212> PRT

<213> Homo Sapiens

<400> 148

Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu
1				5				10						15	
Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp
			20					25					30		
Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe
		35					40					45			
Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr							
50						55									

<210> 149

<211> 56

<212> PRT

<213> Homo Sapiens

<400> 149
 Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn
 1 5 10 15
 Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
 20 25 30
 Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 35 40 45
 Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55

<210> 150
 <211> 55
 <212> PRT
 <213> Homo Sapiens

<400> 150
 Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile
 1 5 10 15
 Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
 20 25 30
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 35 40 45
 Ala Gly Leu Pro Glu Lys Tyr
 50 55

<210> 151
 <211> 54
 <212> PRT
 <213> Homo Sapiens

<400> 151
 Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
 1 5 10 15
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 20 25 30
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 35 40 45
 Gly Leu Pro Glu Lys Tyr
 50

<210> 152
 <211> 53
 <212> PRT
 <213> Homo Sapiens

<400> 152
 Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg
 1 5 10 15
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
 20 25 30
 Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
 35 40 45
 Leu Pro Glu Lys Tyr
 50

<210> 153
 <211> 52
 <212> PRT
 <213> Homo Sapiens

<400> 153

Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
 1 5 10 15
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 20 25 30
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 35 40 45
 Pro Glu Lys Tyr
 50

<210> 154
 <211> 51
 <212> PRT
 <213> Homo Sapiens

<400> 154
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 1 5 10 15
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 20 25 30
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 35 40 45
 Glu Lys Tyr
 50

<210> 155
 <211> 51
 <212> PRT
 <213> Homo Sapiens

<400> 155
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 1 5 10 15
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 20 25 30
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 35 40 45
 Glu Lys Tyr
 50

<210> 156
 <211> 49
 <212> PRT
 <213> Homo Sapiens

<400> 156
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 1 5 10 15
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 20 25 30
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 35 40 45
 Tyr

<210> 157
 <211> 48
 <212> PRT
 <213> Homo Sapiens

<400> 157
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 1 5 10 15

Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser
			20					25					30		
Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr
		35					40					45			

<210> 158

<211> 47

<212> PRT

<213> Homo Sapiens

<400> 158

Ile	Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala
1				5					10					15	
Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly
			20					25					30		
Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr	
		35					40					45			

<210> 159

<211> 46

<212> PRT

<213> Homo Sapiens

<400> 159

Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu
1				5					10					15	
Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys
			20					25					30		
Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr		
		35					40					45			

<210> 160

<211> 45

<212> PRT

<213> Homo Sapiens

<400> 160

Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp
1				5					10					15	
Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp
			20					25					30		
Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr			
		35					40					45			

<210> 161

<211> 44

<212> PRT

<213> Homo Sapiens

<400> 161

Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser
1				5					10					15	
Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro
			20					25					30		
Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr				
		35					40								

<210> 162

<211> 43

<212> PRT

<213> Homo Sapiens

<400> 162
 Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu
 1 5 10 15
 Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn
 20 25 30
 His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 163
 <211> 42
 <212> PRT
 <213> Homo Sapiens

<400> 163
 Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala
 1 5 10 15
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 20 25 30
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 164
 <211> 41
 <212> PRT
 <213> Homo Sapiens

<400> 164
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 1 5 10 15
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 20 25 30
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 165
 <211> 40
 <212> PRT
 <213> Homo Sapiens

<400> 165
 Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
 1 5 10 15
 Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 20 25 30
 Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 166
 <211> 39
 <212> PRT
 <213> Homo Sapiens

<400> 166
 Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
 1 5 10 15
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 20 25 30
 Ala Gly Leu Pro Glu Lys Tyr
 35

<210> 167
 <211> 38

<212> PRT

<213> Homo Sapiens

<400> 167

Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala
1				5				10					15		
Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala
			20					25					30		
Gly	Leu	Pro	Glu	Lys	Tyr										
		35													

<210> 168

<211> 37

<212> PRT

<213> Homo Sapiens

<400> 168

Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn
1				5				10					15		
Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly
			20					25					30		
Leu	Pro	Glu	Lys	Tyr											
		35													

<210> 169

<211> 35

<212> PRT

<213> Homo Sapiens

<400> 169

Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp
1				5				10					15		
Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro
			20					25					30		
Glu	Lys	Tyr													
		35													

<210> 170

<211> 34

<212> PRT

<213> Homo Sapiens

<400> 170

Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly
1				5				10					15		
Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu
			20					25					30		
Lys	Tyr														

<210> 171

<211> 33

<212> PRT

<213> Homo Sapiens

<400> 171

Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg
1				5				10					15		
Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys
			20					25					30		
Tyr															

<210> 172
 <211> 32
 <212> PRT
 <213> Homo Sapiens

<400> 172
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 1 5 10 15
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25 30

<210> 173
 <211> 31
 <212> PRT
 <213> Homo Sapiens

<400> 173
 Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly
 1 5 10 15
 Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25 30

<210> 174
 <211> 30
 <212> PRT
 <213> Homo Sapiens

<400> 174
 Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys
 1 5 10 15
 Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25 30

<210> 175
 <211> 29
 <212> PRT
 <213> Homo Sapiens

<400> 175
 Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp
 1 5 10 15
 Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 176
 <211> 28
 <212> PRT
 <213> Homo Sapiens

<400> 176
 Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro
 1 5 10 15
 Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 177
 <211> 27
 <212> PRT
 <213> Homo Sapiens

<400> 177

Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn
 1 5 10 15
 His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 178
 <211> 26
 <212> PRT
 <213> Homo Sapiens

<400> 178
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 1 5 10 15
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 179
 <211> 25
 <212> PRT
 <213> Homo Sapiens

<400> 179
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 1 5 10 15
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 180
 <211> 24
 <212> PRT
 <213> Homo Sapiens

<400> 180
 Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 1 5 10 15
 Pro Ala Gly Leu Pro Glu Lys Tyr
 20

<210> 181
 <211> 23
 <212> PRT
 <213> Homo Sapiens

<400> 181
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 1 5 10 15
 Ala Gly Leu Pro Glu Lys Tyr
 20

<210> 182
 <211> 22
 <212> PRT
 <213> Homo Sapiens

<400> 182
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 1 5 10 15
 Gly Leu Pro Glu Lys Tyr
 20

<210> 183
 <211> 21

<212> PRT

<213> Homo Sapiens

<400> 183

Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly
1				5					10					15	
Leu	Pro	Glu	Lys	Tyr											
			20												

<210> 184

<211> 20

<212> PRT

<213> Homo Sapiens

<400> 184

Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu
1				5					10					15	
Pro	Glu	Lys	Tyr												
			20												

<210> 185

<211> 19

<212> PRT

<213> Homo Sapiens

<400> 185

Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro
1				5					10					15	
Glu	Lys	Tyr													

<210> 186

<211> 18

<212> PRT

<213> Homo Sapiens

<400> 186

Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu
1				5					10					15	
Lys	Tyr														

<210> 187

<211> 17

<212> PRT

<213> Homo Sapiens

<400> 187

Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys
1				5					10					15	
Tyr															

<210> 188

<211> 16

<212> PRT

<213> Homo Sapiens

<400> 188

Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr
1				5					10					15	

<210> 189
 <211> 15
 <212> PRT
 <213> Homo Sapiens

<400> 189
 Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5 10 15

<210> 190
 <211> 14
 <212> PRT
 <213> Homo Sapiens

<400> 190
 Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5 10

<210> 191
 <211> 13
 <212> PRT
 <213> Homo Sapiens

<400> 191
 Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5 10

<210> 192
 <211> 12
 <212> PRT
 <213> Homo Sapiens

<400> 192
 Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5 10

<210> 193
 <211> 11
 <212> PRT
 <213> Homo Sapiens

<400> 193
 His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5 10

<210> 194
 <211> 10
 <212> PRT
 <213> Homo Sapiens

<400> 194
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5 10

<210> 195
 <211> 9
 <212> PRT
 <213> Homo Sapiens

<400> 195
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5

<210> 196
 <211> 8
 <212> PRT
 <213> Homo Sapiens

<400> 196
 Pro Ala Gly Leu Pro Glu Lys Tyr
 1 5

<210> 197
 <211> 7
 <212> PRT
 <213> Homo Sapiens

<400> 197
 Ala Gly Leu Pro Glu Lys Tyr
 1 5

<210> 198
 <211> 6
 <212> PRT
 <213> Homo Sapiens

<400> 198
 Gly Leu Pro Glu Lys Tyr
 1 5

<210> 199
 <211> 5
 <212> PRT
 <213> Homo Sapiens

<400> 199
 Leu Pro Glu Lys Tyr
 1 5

<210> 200
 <211> 4
 <212> PRT
 <213> Homo Sapiens

<400> 200
 Pro Glu Lys Tyr
 1

<210> 201
 <211> 99
 <212> PRT
 <213> Homo Sapiens

<400> 201
 Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr
 1 5 10 15
 Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His
 20 25 30
 Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp
 35 40 45
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 50 55 60
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 65 70 75 80

Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 85 90 95
 Glu Lys Tyr

<210> 202
 <211> 97
 <212> PRT
 <213> Homo Sapiens

<400> 202
 Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp
 1 5 10 15
 Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg
 20 25 30
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 35 40 45
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 50 55 60
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 65 70 75 80
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 85 90 95
 Tyr

<210> 203
 <211> 99
 <212> PRT
 <213> Homo Sapiens

<400> 203
 Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr
 1 5 10 15
 Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His
 20 25 30
 Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp
 35 40 45
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 50 55 60
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 65 70 75 80
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 85 90 95
 Glu Lys Tyr

<210> 204
 <211> 101
 <212> PRT
 <213> Homo Sapiens

<400> 204
 Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg
 1 5 10 15
 Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr
 20 25 30
 Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly
 35 40 45
 Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg
 50 55 60
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn

65					70					75				80
Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala
				85					90					95
Leu	Pro	Glu	Lys	Tyr										
			100											

<210> 205
 <211> 100
 <212> PRT
 <213> Homo Sapiens

Ser	Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg	Asp	Met	Trp	Arg
1				5					10					15
Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr
			20					25					30	
His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly
		35					40					45		Val
Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg
	50					55					60			Phe
Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn
65					70					75				80
Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly
				85					90					95
Pro	Glu	Lys	Tyr											
			100											

<210> 206
 <211> 99
 <212> PRT
 <213> Homo Sapiens

Phe	Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg	Asp	Met	Trp	Arg	Ala
1				5					10					15
Ser	Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe
			20					25					30	His
Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val
		35					40					45		Trp
Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe
	50					55				60				Phe
Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu
65					70					75				80
Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu
				85					90					95
Glu	Lys	Tyr												

<210> 207
 <211> 98
 <212> PRT
 <213> Homo Sapiens

Leu	Gly	Glu	Ala	Phe	Asp	Gly	Ala	Arg	Asp	Met	Trp	Arg	Ala	Tyr
1				5					10					15
Asp	Met	Arg	Glu	Ala	Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His
			20					25					30	Ala
Arg	Gly	Asn	Tyr	Asp	Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp
		35					40					45		Ala
Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe
	50					55				60				Gly

Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
 65 70 75 80
 Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
 85 90 95
 Lys Tyr

<210> 208
 <211> 97
 <212> PRT
 <213> Homo Sapiens

<400> 208
 Gly Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp
 1 5 10 15
 Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg
 20 25 30
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 35 40 45
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 50 55 60
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 65 70 75 80
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 85 90 95
 Tyr

<210> 209
 <211> 96
 <212> PRT
 <213> Homo Sapiens

<400> 209
 Glu Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met
 1 5 10 15
 Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly
 20 25 30
 Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu
 35 40 45
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 50 55 60
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 65 70 75 80
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85 90 95

<210> 210
 <211> 95
 <212> PRT
 <213> Homo Sapiens

<400> 210
 Ala Phe Asp Gly Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg
 1 5 10 15
 Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn
 20 25 30
 Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala
 35 40 45
 Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala
 50 55 60
 Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly

65					70					75				80
Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr
				85					90					95

<210> 211
 <211> 94
 <212> PRT
 <213> Homo Sapiens

<400> 211

Phe	Asp	Gly	Ala	Arg	Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu
1				5					10					15	
Ala	Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr
			20					25					30		
Asp	Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile
		35					40					45			
Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu
	50					55					60				
Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys
65					70					75					80
Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr		
				85					90						

<210> 212
 <211> 93
 <212> PRT
 <213> Homo Sapiens

<400> 212

Asp	Gly	Ala	Arg	Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala
1				5					10					15	
Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp
			20					25					30		
Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser
		35					40					45			
Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp
	50					55					60				
Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp
65					70					75					80
Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr			
				85					90						

<210> 213
 <211> 92
 <212> PRT
 <213> Homo Sapiens

<400> 213

Gly	Ala	Arg	Asp	Met	Trp	Arg	Ala	Tyr	Ser	Asp	Met	Arg	Glu	Ala	Asn
1				5					10					15	
Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala
			20					25					30		
Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn
		35					40					45			
Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser
	50					55					60				
Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro
65					70					75					80
Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr				
				85					90						

<210> 214

<211> 91
 <212> PRT
 <213> Homo Sapiens

<400> 214
 Ala Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr
 1 5 10 15
 Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala
 20 25 30
 Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala
 35 40 45
 Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu
 50 55 60
 Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn
 65 70 75 80
 His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85 90

<210> 215
 <211> 90
 <212> PRT
 <213> Homo Sapiens

<400> 215
 Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
 1 5 10 15
 Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
 20 25 30
 Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg
 35 40 45
 Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala
 50 55 60
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 65 70 75 80
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85 90

<210> 216
 <211> 89
 <212> PRT
 <213> Homo Sapiens

<400> 216
 Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly
 1 5 10 15
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 20 25 30
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 35 40 45
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 50 55 60
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 65 70 75 80
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 85

<210> 217
 <211> 88
 <212> PRT
 <213> Homo Sapiens

<400> 217

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Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser
 1          5          10          15
Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly
          20          25          30
Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn
          35          40          45
Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
 50          55          60
Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
65          70          75          80
Pro Ala Gly Leu Pro Glu Lys Tyr
          85

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<210> 218
<211> 87
<212> PRT
<213> Homo Sapiens

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```

<400> 218
Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp
 1          5          10          15
Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro
          20          25          30
Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile
          35          40          45
Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
 50          55          60
Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
65          70          75          80
Ala Gly Leu Pro Glu Lys Tyr
          85

```

```

<210> 219
<211> 86
<212> PRT
<213> Homo Sapiens

```

```

<400> 219
Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys
 1          5          10          15
Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly
          20          25          30
Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
          35          40          45
Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 50          55          60
Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
65          70          75          80
Gly Leu Pro Glu Lys Tyr
          85

```

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<210> 220
<211> 85
<212> PRT
<213> Homo Sapiens

```

```

<400> 220
Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr
 1          5          10          15
Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly
          20          25          30
Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg

```

```

      35      40      45
Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
      50      55      60
Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
65      70      75      80
Leu Pro Glu Lys Tyr
      85

```

<210> 221
 <211> 84
 <212> PRT
 <213> Homo Sapiens

```

      <400> 221
Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe
1      5      10      15
His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val
      20      25      30
Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
      35      40      45
Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
50      55      60
Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
65      70      75      80
Pro Glu Lys Tyr

```

<210> 222
 <211> 83
 <212> PRT
 <213> Homo Sapiens

```

      <400> 222
Ser Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His
1      5      10      15
Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp
      20      25      30
Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
      35      40      45
Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
50      55      60
Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
65      70      75      80
Glu Lys Tyr

```

<210> 223
 <211> 82
 <212> PRT
 <213> Homo Sapiens

```

      <400> 223
Asp Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala
1      5      10      15
Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala
      20      25      30
Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly
      35      40      45
Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
50      55      60
Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
65      70      75      80

```

Lys Tyr

<210> 224
 <211> 81
 <212> PRT
 <213> Homo Sapiens

<400> 224
 Met Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg
 1 5 10 15
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 20 25 30
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 35 40 45
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 50 55 60
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 65 70 75 80
 Tyr

<210> 225
 <211> 80
 <212> PRT
 <213> Homo Sapiens

<400> 225
 Arg Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly
 1 5 10 15
 Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu
 20 25 30
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 35 40 45
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 50 55 60
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70 75 80

<210> 226
 <211> 79
 <212> PRT
 <213> Homo Sapiens

<400> 226
 Glu Ala Asn Tyr Ile Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn
 1 5 10 15
 Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala
 20 25 30
 Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala
 35 40 45
 Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly
 50 55 60
 Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70 75

<210> 227
 <211> 78
 <212> PRT
 <213> Homo Sapiens

<400> 227

Ala	Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr
1				5					10					15	
Asp	Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile
			20					25					30		
Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu
		35					40					45			
Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys
	50				55				60						
Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr		
65					70				75						

<210> 228

<211> 77

<212> PRT

<213> Homo Sapiens

<400> 228

Asn	Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp
1				5					10					15	
Ala	Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser
			20					25					30		
Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp
		35					40					45			
Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp
	50				55				60						
Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr			
65					70				75						

<210> 229

<211> 76

<212> PRT

<213> Homo Sapiens

<400> 229

Tyr	Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala
1				5					10					15	
Ala	Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn
			20					25					30		
Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser
		35					40					45			
Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro
	50				55				60						
Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr				
65					70				75						

<210> 230

<211> 75

<212> PRT

<213> Homo Sapiens

<400> 230

Ile	Gly	Ser	Asp	Lys	Tyr	Phe	His	Ala	Arg	Gly	Asn	Tyr	Asp	Ala	Ala
1				5					10					15	
Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala
			20					25					30		
Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu
		35					40					45			
Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn
	50				55				60						
His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr					
65					70				75						

<210> 231
 <211> 74
 <212> PRT
 <213> Homo Sapiens

<400> 231
 Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
 1 5 10 15
 Arg Gly Pro Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg
 20 25 30
 Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala
 35 40 45
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 50 55 60
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 232
 <211> 73
 <212> PRT
 <213> Homo Sapiens

<400> 232
 Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg
 1 5 10 15
 Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu
 20 25 30
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 35 40 45
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 50 55 60
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 233
 <211> 72
 <212> PRT
 <213> Homo Sapiens

<400> 233
 Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly
 1 5 10 15
 Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn
 20 25 30
 Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
 35 40 45
 Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 50 55 60
 Pro Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 234
 <211> 71
 <212> PRT
 <213> Homo Sapiens

<400> 234
 Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro
 1 5 10 15
 Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile
 20 25 30
 Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala

35 40 45
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 50 55 60
 Ala Gly Leu Pro Glu Lys Tyr
 65 70

<210> 235
 <211> 70
 <212> PRT
 <213> Homo Sapiens

<400> 235
 Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly
 1 5 10 15
 Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
 20 25 30
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 35 40 45
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 50 55 60
 Gly Leu Pro Glu Lys Tyr
 65 70

<210> 236
 <211> 69
 <212> PRT
 <213> Homo Sapiens

<400> 236
 Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly
 1 5 10 15
 Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg
 20 25 30
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
 35 40 45
 Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
 50 55 60
 Leu Pro Glu Lys Tyr
 65

<210> 237
 <211> 68
 <212> PRT
 <213> Homo Sapiens

<400> 237
 His Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val
 1 5 10 15
 Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
 20 25 30
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 35 40 45
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 50 55 60
 Pro Glu Lys Tyr
 65

<210> 238
 <211> 67
 <212> PRT
 <213> Homo Sapiens

<400> 238
 Ala Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp
 1 5 10 15
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe
 20 25 30
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 35 40 45
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 50 55 60
 Glu Lys Tyr
 65

<210> 239
 <211> 66
 <212> PRT
 <213> Homo Sapiens

<400> 239
 Arg Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala
 1 5 10 15
 Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly
 20 25 30
 Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
 35 40 45
 Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
 50 55 60
 Lys Tyr
 65

<210> 240
 <211> 65
 <212> PRT
 <213> Homo Sapiens

<400> 240
 Gly Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala
 1 5 10 15
 Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg
 20 25 30
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 35 40 45
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 50 55 60
 Tyr
 65

<210> 241
 <211> 64
 <212> PRT
 <213> Homo Sapiens

<400> 241
 Asn Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu
 1 5 10 15
 Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly
 20 25 30
 Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser
 35 40 45
 Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 242

<211> 63
 <212> PRT
 <213> Homo Sapiens

<400> 242
 Tyr Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala
 1 5 10 15
 Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala
 20 25 30
 Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly
 35 40 45
 Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 243
 <211> 62
 <212> PRT
 <213> Homo Sapiens

<400> 243
 Asp Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile
 1 5 10 15
 Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu
 20 25 30
 Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys
 35 40 45
 Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 244
 <211> 61
 <212> PRT
 <213> Homo Sapiens

<400> 244
 Ala Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser
 1 5 10 15
 Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp
 20 25 30
 Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp
 35 40 45
 Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 245
 <211> 60
 <212> PRT
 <213> Homo Sapiens

<400> 245
 Ala Lys Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn
 1 5 10 15
 Ala Arg Glu Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser
 20 25 30
 Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro
 35 40 45
 Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 50 55 60

<210> 246
 <211> 59
 <212> PRT

<213> Homo Sapiens

<400> 246

Lys	Arg	Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	
1				5				10						15		
Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	
			20					25					30			
Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	
		35					40					45				
His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr						
50						55										

<210> 247

<211> 58

<212> PRT

<213> Homo Sapiens

<400> 247

Arg	Gly	Pro	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg		
1			5					10					15			
Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	
			20				25					30				
Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	
		35					40					45				
Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr							
50						55										

<210> 248

<211> 57

<212> PRT

<213> Homo Sapiens

<400> 248

Gly	Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	
1			5					10					15			
Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	
			20				25					30				
Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	
		35					40					45				
Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr								
50						55										

<210> 249

<211> 56

<212> PRT

<213> Homo Sapiens

<400> 249

Pro	Gly	Gly	Val	Trp	Ala	Ala	Glu	Ala	Ile	Ser	Asn	Ala	Arg	Glu	Asn	
1			5					10					15			
Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	
			20				25					30				
Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	
		35					40					45				
Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr									
50						55										

<210> 250

<211> 55

<212> PRT

<213> Homo Sapiens

<400> 250
 Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile
 1 5 10 15
 Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
 20 25 30
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 35 40 45
 Ala Gly Leu Pro Glu Lys Tyr
 50 55

<210> 251
 <211> 54
 <212> PRT
 <213> Homo Sapiens

<400> 251
 Gly Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln
 1 5 10 15
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 20 25 30
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 35 40 45
 Gly Leu Pro Glu Lys Tyr
 50

<210> 252
 <211> 53
 <212> PRT
 <213> Homo Sapiens

<400> 252
 Val Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg
 1 5 10 15
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
 20 25 30
 Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
 35 40 45
 Leu Pro Glu Lys Tyr
 50

<210> 253
 <211> 52
 <212> PRT
 <213> Homo Sapiens

<400> 253
 Trp Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe
 1 5 10 15
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 20 25 30
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 35 40 45
 Pro Glu Lys Tyr
 50

<210> 254
 <211> 51
 <212> PRT
 <213> Homo Sapiens

<400> 254
 Ala Ala Glu Ala Ile Ser Asn Ala Arg Glu Asn Ile Gln Arg Phe Phe

1		5		10		15
Gly	Arg	Gly	Ala	Glu	Asp	Trp
		20		25		30
Gly	Arg	Ser	Gly	Lys	Asp	Pro
		35		40		45
Glu	Lys	Tyr				
		50				

<210> 255
 <211> 50
 <212> PRT
 <213> Homo Sapiens

	<400>	255
Ala	Glu	Ala
1		5
Arg	Gly	Ala
		20
Arg	Ser	Gly
		35
Lys	Tyr	
		50

<210> 256
 <211> 49
 <212> PRT
 <213> Homo Sapiens

	<400>	256
Glu	Ala	Ile
1		5
Gly	Ala	Glu
		20
Ser	Gly	Lys
		35
Tyr		

<210> 257
 <211> 48
 <212> PRT
 <213> Homo Sapiens

	<400>	257
Ala	Ile	Ser
1		5
Ala	Glu	Asp
		20
Gly	Lys	Asp
		35

<210> 258
 <211> 47
 <212> PRT
 <213> Homo Sapiens

	<400>	258
Ile	Ser	Asn
1		5
Glu	Asp	Ser
		20
Lys	Asp	Pro

35

40

45

<210> 259

<211> 46

<212> PRT

<213> Homo Sapiens

<400> 259

Ser	Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu
1				5					10					15	
Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys
			20					25					30		
Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr		
		35					40					45			

<210> 260

<211> 45

<212> PRT

<213> Homo Sapiens

<400> 260

Asn	Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp
1				5				10						15	
Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp
			20				25						30		
Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr			
		35					40					45			

<210> 261

<211> 44

<212> PRT

<213> Homo Sapiens

<400> 261

Ala	Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser
1				5				10						15	
Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro
			20				25						30		
Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr				
		35					40								

<210> 262

<211> 43

<212> PRT

<213> Homo Sapiens

<400> 262

Arg	Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu
1				5				10						15	
Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn
			20				25						30		
His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr					
		35					40								

<210> 263

<211> 42

<212> PRT

<213> Homo Sapiens

<400> 263

Glu	Asn	Ile	Gln	Arg	Phe	Phe	Gly	Arg	Gly	Ala	Glu	Asp	Ser	Leu	Ala
1				5				10						15	

Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 20 25 30

Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 264
 <211> 41
 <212> PRT
 <213> Homo Sapiens

<400> 264
 Asn Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp
 1 5 10 15
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 20 25 30
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 265
 <211> 40
 <212> PRT
 <213> Homo Sapiens

<400> 265
 Ile Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln
 1 5 10 15
 Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 20 25 30
 Pro Ala Gly Leu Pro Glu Lys Tyr
 35 40

<210> 266
 <211> 39
 <212> PRT
 <213> Homo Sapiens

<400> 266
 Gln Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala
 1 5 10 15
 Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro
 20 25 30
 Ala Gly Leu Pro Glu Lys Tyr
 35

<210> 267
 <211> 38
 <212> PRT
 <213> Homo Sapiens

<400> 267
 Arg Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala
 1 5 10 15
 Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala
 20 25 30
 Gly Leu Pro Glu Lys Tyr
 35

<210> 268
 <211> 37
 <212> PRT
 <213> Homo Sapiens

<400> 268
 Phe Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn
 1 5 10 15
 Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly
 20 25 30
 Leu Pro Glu Lys Tyr
 35

<210> 269
 <211> 36
 <212> PRT
 <213> Homo Sapiens

<400> 269
 Phe Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu
 1 5 10 15
 Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu
 20 25 30
 Pro Glu Lys Tyr
 35

<210> 270
 <211> 35
 <212> PRT
 <213> Homo Sapiens

<400> 270
 Gly Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp
 1 5 10 15
 Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro
 20 25 30
 Glu Lys Tyr
 35

<210> 271
 <211> 34
 <212> PRT
 <213> Homo Sapiens

<400> 271
 Arg Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly
 1 5 10 15
 Arg Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu
 20 25 30
 Lys Tyr

<210> 272
 <211> 33
 <212> PRT
 <213> Homo Sapiens

<400> 272
 Gly Ala Glu Asp Ser Leu Ala Asp Gln Ala Ala Asn Glu Trp Gly Arg
 1 5 10 15
 Ser Gly Lys Asp Pro Asn His Phe Arg Pro Ala Gly Leu Pro Glu Lys
 20 25 30
 Tyr

<210> 273
 <211> 32

<212> PRT

<213> Homo Sapiens

<400> 273

Ala	Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser
1				5				10						15	
Gly	Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr
			20					25					30		

<210> 274

<211> 31

<212> PRT

<213> Homo Sapiens

<400> 274

Glu	Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly
1			5					10						15	
Lys	Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr	
			20					25					30		

<210> 275

<211> 30

<212> PRT

<213> Homo Sapiens

<400> 275

Asp	Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys
1			5					10						15	
Asp	Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr		
			20					25					30		

<210> 276

<211> 29

<212> PRT

<213> Homo Sapiens

<400> 276

Ser	Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp
1			5					10						15	
Pro	Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr			
			20					25							

<210> 277

<211> 28

<212> PRT

<213> Homo Sapiens

<400> 277

Leu	Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro
1			5					10						15	
Asn	His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr				
			20					25							

<210> 278

<211> 27

<212> PRT

<213> Homo Sapiens

<400> 278

Ala	Asp	Gln	Ala	Ala	Asn	Glu	Trp	Gly	Arg	Ser	Gly	Lys	Asp	Pro	Asn
1			5					10						15	
His	Phe	Arg	Pro	Ala	Gly	Leu	Pro	Glu	Lys	Tyr					

20

25

<210> 279
 <211> 26
 <212> PRT
 <213> Homo Sapiens

<400> 279
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 1 5 10 15
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 280
 <211> 25
 <212> PRT
 <213> Homo Sapiens

<400> 280
 Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe
 1 5 10 15
 Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 20 25

<210> 281
 <211> 24
 <212> PRT
 <213> Homo Sapiens

<400> 281
 Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His Phe Arg
 1 5 10 15
 Pro Ala Gly Leu Pro Glu Lys Tyr
 20

<210> 282
 <211> 23
 <212> PRT
 <213> Homo Sapiens

<400> 282
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21770

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 38/00, 39/00; C07H 21/02, 21/04; C07K 5/00, 14/00

US CL :424/184.1; 514/2; 530/300, 350; 536/23.1, 23.4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/184.1; 514/2; 530/300, 350; 536/23.1, 23.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Author search, Wang, Ji-Ming; Oppenheim, Joost J.; Su, Shao-Bo; Gong, Wang-Hua; Gao, Ji-Liang; Murphy, Philip M.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Medline, Biosis, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	SHAO et al. A Seven Transmembrane G Protein Coupled Receptor, FPRL1, Mediates the Chemotactic Activity of Serum Amyloid A for Human Phagocytic Cells. J. Exp. Med. 18 January 1999, Vol. 189, No. 2, pages 395-402	1-10 ----- 11-28
X -- Y	WANG J.M. et al. A Seven Transmembrane, G Protein Coupled Receptor FPRL1, Mediates the Chemotactic Activity of Serum Amyloid A for Human Phagocytic Cells. In:FASEB J., Experimental Biology, 27 April, 1999, Vol. 13, No. 5, part 2, A656.	1-10 ----- 11-28
X ----- Y	LE Y, et al. A New Insight into the Role of "Old" Chemotactic Peptide Receptors FPR and FPRL1: Down-Regulation of Chemokine Receptors CCR5 and CXCR4. Forum. October 1999. Vol. 9, No. 4, pages 299-314.	1-10 ----- 11-28

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 29 FEBRUARY 2000	Date of mailing of the international search report 06 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON L. TURNER Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21770

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DENG X, et al. A Synthetic Peptide Derived From Human Immunodeficiency Virus Type 1 gp120 Downregulates the Expression and Function of Chemokine Receptors CCR5 and CXCR4 in Monocytes by Activating the 7-Transmembrane G-Protein-Coupled Receptor FPRL1/LXA4R. Blood. 15 August 1999. Vol. 94, No. 4, pages 1165-73.	1-10
X	SHAO Bo Su, et al. T21/DP107, A Synthetic Leucine Zipper-Like Domain of the HIV-1 Envelope gp41, Attracts and Activates	1-10
--	Human Phagocytes by Using G-Protein-Coupled Formyl Peptide Receptors. 19 May, 1999. Vol. 162, pages 5924-30.	-----
Y		11-28